1 Introduction

In contrast to soluble chemical agents that act after dissolution and may cause toxic effects in the human body on the molecular level, airborne particles in workplace atmospheres are frequently associated with chronic occupational health effects due to a long biopersistence of almost insoluble respirable dust particles deposited in the pulmonary region of the lung. Common examples are coal dusts causing pneumoconiosis, crystalline silica inducing silicosis, and asbestos leading to asbestosis and lung cancer. In all cases of chronic exposures, the deposited particles are accumulated and redistributed among the pulmonary subcompartments and the lung-associated lymph nodes, and they may be retained there for a considerable length of time even when exposures are discontinued.

To the extent that the particles are contained in mobile alveolar macrophages on the alveolar surface, they may gradually be removed from the alveolar region by macrophage-mediated intracellular particle transport to the mucociliary escalator of the tracheobronchial tree. This transport by macrophages constitutes the classical alveolar clearance pathway. However, compared to the tracheobronchial clearance with its dedicated mechanism of mucous transport by the synchronized action of ciliated epithelial cells, alveolar clearance is not very effective. While tracheobronchial clearance removes deposited particles from the conducting airways essentially within about one day, the fastest alveolar clearance as seen in small rodents does not relieve the alveolar region by more than 2 % per day of the macrophage pool burden. This

transfer is mediated by a marginal daily migration of mobile alveolar macrophages to the tracheobronchial tract.

Some investigators believe that a fraction of the particles that escapes phagocytosis and penetrates into the interstitial space may be returned to the alveolar surface or the tracheobronchial tract and thus become again available for alveolar and tracheobronchial clearance. However, the major fraction of the particles escaping from the alveolar surface to other pulmonary subcompartments seems to be no longer available for macrophage-mediated clearance whivh provides final removal from the body. Instead, these particles will, if at all, most likely be internally removed from the pulmonary region via the lymphatics to the lung-associated lymph nodes.

While it is easy to associate the effective dose of a dissolved toxic agent with its mass or its concentration in the body, the long-term effects of biopersistent particles must be the result of a sequence of complex mechanisms that may not be the same for fibers of asbestos and isometric particles like quartz, but, if nongenotoxic, epigenetic carcinogenesis of lung cancer is considered, the mechanisms most probably involve elements of unspecified heterogeneous surface reactions or catalyses.

Obviously, the application of conventional multistage models of chemical carcinogenesis is unsuitable for biopersistent particles as the dose rate characteristics in those models are determined by the administration of constant daily mass doses. This does not apply to particle inhalation despite a constant daily deposition rate, because the daily clearance is increasing with increasing particle burdens of the alveolar macrophages. Thus the daily increments of pulmonary lung burden must successively

diminish unless the macrophage mobility is significantly impaired. A quantitative assessment of these effects seems to be feasible for rats by employing an adequate pulmonary retention model. However, up to date, no approach to health risk assessments of chronic exposures to biopersistent particles has been published that would justify the claim that an appropriate retention model was used. This applies to pulmonary particle retention models as well as to carcinogenicity models that fail to relate to particle retention.

2 Choosing a Pulmonary Retention Model for Biopersistent Particles

In a forthcoming review,[1] examples of retention models described in the literature were categorized according to DiStefano and Landaw[2] as models of data and models of systems.

Models of data are basically data-reducing models employing mathematical functions with little or no mechanistic relevance to the retention process. They represent empirical data over a documented experimental range by best fit. Thus by principle, models of data are interpolation models which should not be applied outside the range they were derived from. Most models in the literature belong to this category. Some of them were derived only from postexposure retention data but nevertheless applied to predict results of chronic exposures.

Models of systems have a better chance of being reliable in extrapolations. With-

out exception, they employ multicompartmental designs for the pulmonary region of the lung, and the compartments are linked together by a system of kinetic differential equations. The review of available retention models revealed that none of the scrutinized models where without drawbacks, but the physiology-based compartmental kinetics (POCK) model[3] has successfully modeled subchronic and chronic rat exposure data of more than 25 exposure runs with diesel exhaust, carbon black, xerographic toner, and titanium dioxide at exposures equivalent to ubiquitous environmental concentrations between 40 and 6 000 $\mu g/m^3$ of particulate air pollution. Primary particle diameters varied between 0.025 and 4.0 μm. To date, this performance record is by far more extensive than for two other models of systems found in the literature. No claim is made that this proves the POCK model to be superior, but it is certainly much better validated. Figure 1 gives the block diagram of the model design. Details of the design are given in a comprehensive publication of a standard version of the model.[3] Performance tests are published elsewhere.[4–8]

The POCK model employs six physiological parameters which remain constant in all simulations regardless of employed exposure aerosol and exposure conditions. However, there are seven more parameters which may be different for different aerosols and rat strains. Their changes must be determined by intuition, plausible comparative considerations, and trial and error. Before being accepted, the final choice must give good simulations for all available exposure modes such as high and low exposure concentrations, subchronic exposures with data collection continued during the pos-

texposure period, and chronic exposures.

The model value of the deposition rate must be determined by best fit. The compatibility of the obtained best-fit value with deposition rates obtained in independent experiments is used as a quality criterion. The computer-assisted solution of a maximum of 105 differential equations gives particle mass load distributions in alveolar macrophages, distributions of free particle clusters on the alveolar surface, and seven compartmental particle mass contents.

Until recently, not more than two of these compartmental burdens, *viz.*, total pulmonary lung burden, M_{alv}, and lung-associated lymph node loads, M_{LN}, were acquired in experimental rat studies and have been used for POCK simulations, while the remainder of the model data remained hypothetical. To date, however, a few additional experimental rat data became available in a study with titanium dioxide[9] giving indirectly some results for the macrophage burden and the retention in the interstitial space. These data were consistently modeled in POCK simulations[7] and gave limited evidence for the theoretical POCK model predictions of retention in the macrophage pool and in the interstitial space.

The model applies to rats only. It is probably inappropriate to expect that the POCK model can provide reliable data for other species such as mouse and man by supplying merely different data to the model parameters. Besides the changes in parameter values, the mechanistic assumptions of the rat model may also change when going to another species. For instance, the rat model seems to work well with

the model assumption that macrophage recruitment runs at a maximum so that the macrophage population is almost constant during the whole exposure run. This has been questioned to be true and could let the model fail for mice or humans as the assumption for rats may no longer be tenable for mice and humans.

3 Lung Overload of Biopersistent Particles is a Predictable Phenomenon and not a Common Threat of Particulate Air Pollution

The kinetic system of macrophage-mediated alveolar clearance is basically represented by

$$\frac{dM}{dt} = D_{ep} - \kappa M \tag{1}$$

where M is the mass contained in the alveolar pool of macrophages, κ is the coefficient of the classical clearance rate, and D_{ep} is a constant dust deposition rate given, for instance, in $\mu g/day$. Normally, this system of constant daily deposition approaches a steady state that would be established for

$$D_{ep} = \kappa M \tag{2}$$

when in the course of time the load of the macrophage pool has increased sufficiently so that the daily clearance rate, κM, finally compensates the constant daily deposition, D_{ep}. This is shown in Figure 2 to happen after some 350 days. However, there are obvious limits to achieving this equilibrium. For instance, if the deposition rate, D_{ep}, is unusually high, the equilibrium may require a macrophage pool load exceeding the finite load capacity of the pool, M_{max}. This is the basic explanation for the

experimentally found particle overload of the lung in animal exposure studies at high deposition rate. It implies merely the single, plausible assumption that the number and the load capacity of the macrophages is not infinite. Then, at some point in time, the macrophages can no longer accumulate any additional particles, the clearance rate is confined to κM_{max}, and any excess of the continuing daily particle deposition has to go to other pulmonary subcompartments. Thus the total pulmonary particle load continues to rise.

This is quantitatively born out for rats in the POCK model simulations of various inhalation exposure studies with biopersistent aerosols. By adopting and modifying a viable hypothesis by Morrow[10] linking alveolar clearance to both the mobility of alveolar macrophages and their finite number and capacity to function under acquired particle burdens, the POCK model appears to be capable of covering all accessible and applicable experimental exposure concentrations in inhalation studies with rats and biopersistent particles. This was facilitated by assuming that the clearance rate coefficient, κ, is not a constant but a decreasing function of advancing rat age and rising particle volume loads incorporated by and distributed among the macrophages of the alveolar pool.

A three-dimensional graph in Figure 3 shows the POCK interpretation of the results obtained in lifetime exposures of rats to diesel exhaust.[11] The vertical axis represents the pulmonary burden relative to the deposition rate, *i.e.*, in proportion to the exposure concentration. The percentage scale refers to the theoretical steady-state retention expected for first-order kinetics (see Figure 2). The horizontal axes

refer to exposure time and exposure concentration. The latter relates to equivalents of ubiquitous environmental concentrations, and the graph accentuates the low exposure regime by using a logarithmic scale. For exposure concentrations up to more than 100 $\mu g/m^3$, the relative retention patterns remain unchanged, *i.e.*, for any point in time, the pulmonary burdens and the exposure concentrations are directly proportional. In this region, rat data from lifetime exposures of 73 $\mu g/m^3$ showed lung tumors in only 1.3 % of the rats. This percentage does not exceed the species-specific spontaneous lifetime tumor incidence. In the overload regime, however, rat data for lifetime exposures to 730 $\mu g/m^3$ showed lung tumors in 3.6 % of the rats. Of all the rat studies with diesel exhaust reported to date, this is the lowest statistically significant experimental value in excess of the spontaneous rat lung tumor incidence. The corresponding time pattern in the graph is marked by arrows. At lifetime exposures to 1 460 $\mu g/m^3$, which is the highest concentration shown in the graph, the tumor rate increased to 12.8 % of tumor-bearing rats.

The particle burdens relative to the exposure concentration may be compared in Figure 4, which shows the time patterns for the total pulmonary region, M_{alv}, the pool of alveolar macrophages, M_{PT}, the interstitial space, M_{IT}, and the lung-associated lymph nodes, M_{LN}, in the low exposure regime. The theoretical data are obtained by extrapolation to an environmental exposure concentration of 1 $\mu g/m^3$ and by interpolation to 140 $\mu g/m^3$. The proportionality to the exposure concentration in the low exposure range that is seen for the pulmonary burden in Figure 3, applies also to

the subcompartments of the pulmonary region and the lung-associated lymph nodes. The respective relative retention curves for the two borderline exposure concentrations are almost identical although the absolute loads vary by a factor of 140. Thus, the corresponding graph of absolute data in Figure 5 shows all curves of the 1 $\mu g/m^3$ exposure running very closely along the abscissa.

The time pattern of the total pulmonary burden, M_{alv}, which is usually available in all rat exposure studies of the retention of biopersistent particles, permits a plausible explanation: The pattern shows first the characteristics seen for first-order kinetics (Figure 2) but the asymptotic approach to a steady state is replaced by an eventual increase of the pulmonary burden between some 200 and 730 days of exposure which is caused by a gradual decline of the clearance rate coefficient, κ, in aging rats by some 30 % over their lifetime.[12]

For the overload range beginning at exposure concentrations exceeding about 150 $\mu g/m^3$, the situation changes rapidly. Figure 6 shows the total pulmonary burdens still plotted in relative terms after lifetime exposure against environmental concentrations on a linear abscissa. A graph analogous to Figure 4 for the overload regime would show a clutter of intersecting curves due to the prominent disproportionalities of the changes in compartmental retention between exposures at 140 and 1 460 $\mu g/m^3$. Therefore, Figures 7 and 8 show the actual mass burdens for the two border concentrations separately. When comparing the respective patterns of the two graphs, the difference in the ordinate scales should be observed. In absolute terms, the tenfold

increase of exposure in this range causes a 19-fold increase of the total pulmonary burden over the lifetime of the rats.

Contrary to the low exposure regime, the subcompartments in the pulmonary region show entirely different growth rates. While macrophage sequestration, M_{SQ}, amounts to a negligible mass of 7.5 μg of trapped particles in 730 days at 140 $\mu g/m^3$, that particle mass increases by almost two orders of magnitude to 645 μg in 730 days at 1 460 $\mu g/m^3$. However, the total particle mass in all macrophages, M_{PT}, rises merely by a factor of 6 from 430 to 2 600 μg. The biggest absolute mass increase is found for the interstitial mass burden, M_{IT}, which rises from a modest amount of 600 μg to 16 250 μg by a factor of 27, thus constituting 84 % of the total pulmonary burden.

Apparently, the simple but plausible interpretation of particle overload by Equations 1 and 2 implying macrophages getting saturated with incorporated particles and being unable to phagocytize particles beyond a maximum load, M_{max}, seems to remain valid not only for the simplified case that the macrophage-mediated clearance is not impaired before all macrophages are saturated with particles, but also for the POCK model design where the macrophage turnover by death and recruitment and the mobility decline with increasing load will never facilitate macrophage burdens anywhere near the theoretical maximum load, M_{max}, of the alveolar pool. Even in severe overload situations, the burden of the macrophage pool, although growing with increasing exposure concentration, seems to reroute or unload the excessive deposition

to the interstitial compartment way before the pool of macrophages acquires burdens closely approaching the theoretical maximum, M_{max}. As expected, particle overload still causes an unusually high burden in macrophages (Figure 9), but the bulk of the excessive and continuous particle deposition during lifetime studies seems to end up in the *interstitium*.

Figure 7 gives the time patterns of the compartmental burdens at the beginning of the overload regime. For the beginning of overload, total pulmonary lung burdens have been typically estimated to be about 1 mg per rat lung or per gram of rodent lung.[10,13] Interestingly, even in this rather regular case of retention (see Figure 4), the interstitial burden at the end of the lifetime seems to represent slightly more than 50 % of the total alveolar burden, M_{alv}. However, in absolute terms, this burden amounts to only 0.6 mg which seems negligible compared to the 16.6 mg retained at the end of the lifetime for exposures to 1 460 $\mu g/m^3$.

There are indications that, in the past, coal miners may actually have worked under conditions causing lung overload with coal dust. Postmortem analyses of German coal miner lungs revealed interstitial dust deposits in excess of 50 grams per lung.[14]

For the general public, however, even when exposed to heavy particulate air pollution levels, lung deposits may not get anywhere near an overload situation, and health effects observed in animal experiments under overload conditions should not be extrapolated to deposition rates that can never produce particle overload in the lung.

For low deposition rates, an overload situation is not simply delayed and achieved later. Since the kinetic system can actually cope with low deposition rates, it will establish a quasisteady state for the total pulmonary burden as indicated by the pattern in Figure 4.

Impressive as the effects of particle overload on retention in Figures 3, 6 and 8 may look, it is a fairly safe guess that for the public and for most of the occupational scenarios of today an ubiquitous permanent level of particulate air pollution at 150 $\mu g/m^3$ or more is in considerable excess of actual ambient and occupational field data. Thus, if humans are not considerably more sensitive than rats, they should be virtually safe from developing particle overload in their lungs in their lifetime.

Even if this qualitative assessment is questioned, it would be prudent to focus modeling efforts on retention patterns that are not influenced and overemphasized by an overload retention of biopersistent particles. The POCK model should be favored not so much because it can cope with overload scenarios but because it models the redistribution of alveolar deposits in the pulmonary subcompartments in the physiologically regular range of unimpaired pulmonary lung clearance.

4 A Hypothesis of an Effective Relative Dose for Biopersistent Particles

The basis for a hypothesis of a specific effectice relative dose for lung cancer in rats by particle overload consists of two theoretical assumptions. The obvious one is the

simple recognition that an insoluble particle can only interact with its biological environment by way of its size and shape or by the structure and chemistry of its surface. In case of overload carcinogenesis, a chemical specificity seems unlikely because chemically entirely different particles such as carbon black and titanium dioxide lead to the same lung tumors in rats. Therefore, the chemically unspecific physical adsorption to common atomic surface inhomogeneities of a particle may provide the means for certain biomolecules to change their activity either permanently after contact or while in the adsorbed state. In general terms, this can be described as a surface reaction or surface catalysis that produces altered biomolecules at a particular rate. In a specific tissue or cell, this rate could then lead to biologic lesions on the molecular level. As the surface provides a certain reaction rate, the effevtive dose would then be a time integral over the time the surface resides in the target tissue or target cells.

The other assumption is suggested by the simulation results of the POCK model which were discussed in the preceding section. Figure 8 reveals that, with the onset of particle overload, which in the shown example occurs after about two months, the increase of the total pulmonary burden is paralleled by an enormous increase of the interstitial burden. So it is not too far fetched to assume that the target tissue for the rat-specific overload carcinogenesis is a location in the interstitial space. In the POCK model, this space includes the interior of the alveolar walls with the layer of epithelial cells as the most likely candidate as the focus of lesions.

Time integrals after a single mass administration or over continuous daily mass applications of toxic agents as a measure of effective relative dose are not unusual in

toxicology. They are known as the area under the curve (AUC) of the time pattern of a mass burden (most freqently expressed as a concentration per body weight or body fluid). Mechanistically, for instance, areas under the curve become significant when the absorption of a drug is rate-limited and there is a competing clearance mechanism. However, a radiation dose from radioactive particles deposited in the lung is always a time integral because the decay of the radioisotopes provides only a rate of a radiation dose. This decay rate is, of course, proportional to the particle mass which, therefore, becomes part of the intensity parameter for the time integration defining an effective *relative* dose. An effective *relative* dose is merely proportional to the real effective dose, for which some other, supposedly constant factors remain unknown.

In the time integral suggested here for biopersistent particles, the particle mass becomes part of the intensity parameter which, in this case, is the surface reaction rate. With the pulmonary *interstitium* as the sensitive target tissue, an effective relative dose can be formulated mathematically.

In a homogeneous particle population deposited in the *interstitum* of the rat lung, the total surface of this population is

$$A = S \times M_{IT} \tag{3}$$

where S is the specific surface area of the subcompartmental particle mass, M_{IT}. This surface must be associated with an effective dose rate determined by a rate coefficient, ν, of a heterogeneous surface catalysis that converts a biological substrate, X, of a concentration C_x to a catalytic product, Y, of a concentration C_y. A toxic effect could

then be triggered by either the reduction of the concentration C_x or the occurrence of the catalytic product compound Y.

Kinetically, a first-order reaction would give

$$\frac{d\,C_y}{dt} = S \times M_{IT} \times \nu \times C_x \tag{4}$$

and if no competing removal process for the compound Y interferes, the effective dose would be

$$\int_{t_o}^{t_1} \frac{d\,C_y}{dt} dt = S \times \nu \int_{t_o}^{t_1} M_{IT} \times C_x dt \tag{5}$$

where the rate coefficient, ν, and the substrate concentration, C_x, remain unknown but can be assumed to be constant. Then, the residual factor

$$\mathcal{D}_{eff_{rel}} = S \times \int_{t_o}^{t} M_{IT}\, dt \tag{6}$$

may be called an effective relative dose.

5 A Hypothesis of a Threshold for Overload Carcinogenesis

The stagnation of particle deposits in lung-associated lymph nodes in the presence of rat lung tumors due to overload carcinogenesis was recognized as a regular occurrence in a variety of exposure studies.[8] Thus, the stagnation (see Figure 8) was taken as an indicator of lung tumor induction. This led to a hypothesis of a critical dose for rat lung overload carcinogenesis which was modeled and tested by means of POCK simulations that used the time integral over the interstitial retention as an effective relative dose. Specific minimum values dependent on aerosol and rat strains

were obtained which could be semiquantitatively be confirmed by calculating empirical dose-response relationships in terms of time integrals over the interstitial mass retention. Figure 10 shows the empirical data and their extrapolation to the level of spontaneous tumor incidences. For diesel exhaust, the POCK model threshold values were 1600, 2400, and 4000 $mg \times days$ for Fischer 344, Fischer 344/N, and Wistar rats, respectively. With carbon black, a common value of 400 $mg \times days$ was obtained for Fischer 344/N and Wistar rats. Finally, anatase titanium dioxide gave a value of 4100 $mg \times days$ for Wistar rats,[7] but there were insufficient experimental data to compare the latter value to an empirical dose-response relationship. The POCK model threshold values may be subject to changes with better experimental data, but they all fall into the range found for the empirical dose-response data. At present, the significance of the results is that all values obtained are positive. Thus, they indicate thresholds. These findings support the effective relative dose definition for the retention in the pulmonary *interstitium* as well as the threshold assumption for overload carcinogenesis of lung tumors in rats. As the employed aerosols, *i.e.*, diesel exhaust, carbon black, and anatase titanium dioxide, were of primary sizes in the submicronic range, the findings may be valid for these sizes only.

6 A Probit Analysis of Lung Tumors by Overload Carcinogenesis in Rats

Usually, experimental studies of particular exposure aerosols do not yield a unique dose-response curve. Results vary easily between different laboratories due to different

conditions of housing, feeding and other specifics of animal caretaking and operating conditions. Therefore to maintain consistency, the respective dose-response lines in Figure 10 were derived exclusively from specific studies conducted simultaneously in multiple exposure runs in the same laboratory. Consequently, different results for different strains and different aerosols could also involve to some degree differences between exposure facilities in different laboratories.

For the four studies represented in Figure 10, a probit analysis shows that the studies probably belong to the same type of dose-response relationship so that strain, aerosol, and exposure facility have only a factorial influence. Unfortunately, the experimental dose-response data represent in each case merely the minimum necessary for an analysis, and they gain only slightly by the number of studies. Figure 11 shows the tumor incidence rate data reduced by the spontaneous tumor incidence rate in a probability grid with a logarithmic abscissa for the effective relative dose adopted above. The similar slopes of the four lines indicate a close relationship that can be represented by a common log-normal cumulative distribution function

$$F(c) = \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{c} e^{-\frac{c^2}{2}} dc \qquad (7)$$

with the argument

$$c = \frac{\log \mathcal{D}_{rel}(t_{end}) - \log \mathcal{D}_{rel_{50\%}}}{\sigma_{log}} \quad , \qquad (8)$$

relating the lifetime dose variable, $\mathcal{D}_{rel}(t_{end})$, to the relative lifetime dose $\mathcal{D}_{rel_{50\%}}$ at $F(c) = 0.50$ and the geometric standard deviation, σ_{log}.[1]

Then, a formal evaluation yields data for the four studies as represented in Table 1. The individual data for the geometric standard deviation, σ_{log}, and the relative lifetime dose, $\mathcal{D}_{rel_{50\%}}$, at $F(c) = 0.50$, have a weak base. Substituting these individual data by the values for Fischer 344 rats as an average, the three other studies can then be characterized by their respective factor, K, as listed in Table 1. This gives individual relative doses for the 50 % excess risks as

$$\mathcal{D}_{rel_{50\%}} = K \times \mathcal{D}^{(1)}_{rel_{50\%}} \tag{9}$$

For $c = -4.75$ in Equation 8, the tumor excess risks fall below 1×10^{-6}, a value that is generally considered to be virtually safe. With the individual data of Table 1, the virtually safe risk corresponds to the values $\mathcal{D}_{rel}(t_{end})$ given in Table 2. These values of the effective relative lifetime doses as defined previously correspond to values of the experimental exposure rate index, EI in $mg/m^3 \times hr/week$, and the ubiquitous environmental particle mass concentration, C_{env} in $\mu g/m^3$, that are also listed in Table 2.

The individual numbers obtained differ in their virtually safe risk assessment by less than a factor of 5 and give a virtually safe minimum value for the ubiquitous diesel soot concentration of $C_{env} < 40\ \mu g/m^3$. The present data base may not yet permit firm conclusions, but compared to the experimental dose-response rat data in Figure 10 and corresponding POCK model evaluations, all of which suggest a no-effect threshold at very much higher relative doses, this no-threshold approach to a

virtually safe dose is very conservative for a nongenotoxic carcinogen.

7 The Environmental Exposure Regime

The POCK model evaluations of experimental rat exposure data for ubiquitous exposure concentrations below 140 $\mu g/m^3$ suggest that the retention in the total pulmonary region and in all active subcompartments of the region is proportional for different exposure concentrations and almost exclusively defined by exposure time. No retention occurs in the subcompartment for irreversible interstitial deposition, M_{IG}. Similarly, even at the upper end of the environmental exposure range, the particle load of the subcompartment of sequestered macrophages, M_{SQ}, may be neglected as it acquires less than 2 % of the total particle mass, M_{PT}, incorporated by the pool of macrophages. Furthermore, as demonstrated in Figure 12, the observed proportionality of all other subcompartmental retention patterns to the deposition rate for a given time in this range applies also to the time-integrated dose (Equation 6) and the maximally possible dose, $D_{ep} \times \frac{t^2}{2}$.

As shown in Figure 13, this is again in contrast to the upper exposure regime. Approaching overload conditions, the dose ratio splits up to increased percentages with increasing deposition rate, D_{ep}.

The proportionalities within the environmental exposure regime facilitate a simplification of the POCK model for environmental applications. Figure 14 shows corresponding time patterns for the ratio between the effective relative dose, $\mathcal{D}_{rel}(t)$, and

the deposition rate, D_{ep} for exposure concentration between 1 and 140 $\mu g/m^3$. The curves follow an almost unique pattern with slight differences towards the lifetime end of the rats where the highest deposition rate corresponding to an exposure to 140 $\mu g/m^3$ causes a relative increase of less than 10 %. Apparently, the influence of the macrophage burden on macrophage mobility, which is an essential feature of the POCK model in the overload range, may be practically ignored in the environmental exposure range when the exposure aerosol is diesel exhaust. The model would then produce the lowest of the curves in Figure 14. Qualitatively, this finding can probably be generalized.

Dose applications in carcinogenesis models require a dose rate of the carcinogen under consideration. Most commonly, a constant daily dose is used. In fact, today's linearized multistage models of carcinogenesis are consistent only under the assumption of a constant daily dose. According to the definition of effective relative dose introduced in Section 4, the dose rate corresponds to the derivative of Equation 6. Therefore, it is proportional to the retention in the *interstitium*, M_{IT}. Since the interstitial retention increases with exposure time, the retention results of chronic animal exposure studies cannot be related to tumor incidences by presently used linearized multistage models that require constant daily doses.

For carcinogenesis models not requiring constant dose rates, a simple numerical relationship between dose rate and deposition rate can be provided by the POCK model. As demonstrated in Figure 4, the interstitial retention divided by the deposition rate is another almost unique function of exposure time. This function, $Q(t)$,

and its limited variability is shown in Figure 15. The effective relative dose rate is then according to Equation 6

$$\frac{d\mathcal{D}_{eff_{rel}}}{dt} = S \times D_{ep} \times Q(t) \tag{10}$$

and it would be easy to assume an average pattern for the Function, $Q(t)$, and calculate an approximation formula for it.

8 Conclusions

The POCK model was used as an example of a physiologically based system model of pulmonary retention of insoluble particles in rats that has a good record of validation by various experimental data. The analysis of the model simulation of experimental data shows that the overload phenomenon can be explained as a common feature in aerosol inhalation studies with animals whenever the particles are practically insoluble, possibly of submicron size, and the exposure concentration is excessive. However, an ambient concentration up to about 150 $\mu g/m^3$ of airborne respirable diesel soot does not cause essential overload in rats. This indicates that overload in rats will not occur within the environmental range of ambient particulate air pollution. Actual pulmonary retention in rats can be simulated without accounting for alveolar macrophage impairment. Furthermore, as lung tumor induction in rats by diesel soot, carbon black and titanium dioxide is always associated with lung overload, the model provides a theoretical no-effect threshold for overload carcinogenesis. A no-threshold probit analysis of chronic exposure studies of different rat strains to diesel

soot and carbon black suggests that exposures to these aerosols have an excess of relative risk ranging below 1×10^{-6} for chronic ambient exposure concentrations of at least 40 $\mu g/m^3$ of diesel soot or less. This indicates a "virtually safe" level and is a very conservative estimate.

Based on a plausible physicochemical assumption about the interaction of insoluble particles with their biological environment, the model permits the derivation of a relationship between a constant daily deposition rate of insoluble particles in the rat lung and the time-dependent effective relative dose rate of the retained particles. As the effective relative dose is an area-under-the-curve type dose, its dose rate increases with time in proportion to the interstitial retention. However, presently used linearized multistage models of cancer incidence require constant daily doses. Therefore, they are not suited to evaluate aerosol exposure studies with regard to the carcinogenic effects of insoluble particles. Obviously, the desirable reliability can only be achieved if future efforts utilize realistic retention models and more flexible and properly adjusted models of carcinogenesis.

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Table 1 : Graphically Determined Standard Deviations, σ_{log} ,
of Log-Normal Relative Lifetime Dose *versus* Lung Tumor Probability, $F(c)$,
due to Particle Overload Carcinogenesis in Rats

Rat Strain	Fischer 344	Fischer 344/N	Wistar	Fischer 344/N
Aerosol	Diesel Exhaust			Carbon Black
σ_{log}	0.50	0.54	0.64	0.47
$\mathcal{D}_{rel_{50\%}}$	20200	76000	63800	31800
Factor K	1	3.8-2.9	3.2-1.1	1.6-2.1

Table 2 : Maximum Values for the Exposure Rate Index, EI ,
the Relative Lifetime Dose, $\mathcal{D}_{rel}(t_{end})$,
and the Ubiquitous Particle Mass Concentration, C_{env} ,
Not Exceeding the "Virtually Safe" Excess Risk of 1×10^{-6}
According to the Four Dose-Response Lines of Figure 11.

Parameter	Dimension	Diesel Exhaust			Carbon Black
Rat Strain		Wistar	Fischer 344	Fischer 344/N	Fischer 344/N
EI	$mg/m^3 \times hr/week$	6.9	12.3	14.2	30.8
$\mathcal{D}_{rel}(t_{end})$	$mg \times days$	58	85	207	186
C_{env}	$\mu g/m^3$	41	73	85	183

LEGENDS for FIGURES 1 to 15

Figure 1: Physiology–Oriented Compartmental Kinetics Model of Retention of Inhaled Insoluble Particles in Rats.

(Courtesy of Raven Press)

Figure 2: Typical First-Order Mass Retention Kinetics of Deposited Insoluble Particles in the Alveolar Region of the Lung

Retention under Chronic Deposition Rate, D_o (0.0693 mg/day)

Clearance Rate Coefficient $\kappa = 0.01386\ day^{-1}$

(Courtesy of Raven Press)

Figure 3: POCK Simulation of Alveolar Lung Burdens Relative to a Standard Maximum Lung Burden (see text) in Rats Chronically Exposed to Diesel Exhaust Between 1 and 1460 $\mu g/m^3$ for Lifetime (730 days);

Experimental Data Base by Mauderly.[11]

Figure 4: POCK Simulation of Total and Subcompartmental Pulmonary Retention in Rat Lungs Relative to a Standard Maximum Lung Burden (see text) During Chronic Exposure to Diesel Exhaust at 1 and 140 $\mu g/m^3$ for Lifetime (730 days);

(M_{alv} Total Pulmonary Load, M_{IT} Total Interstitial Load, M_{PT} Total Alveolar Macrophage Load, M_{LN} Lymph Node Load)

Experimental Data Base by Mauderly.[11]

Figure 5: POCK Simulation of Total and Subcompartmental Pulmonary Particle Mass Retention in Rat Lungs During Chronic Exposure to Diesel Exhaust at 1 and 140 $\mu g/m^3$ for Lifetime (730 days);
(M_{alv} Total Pulmonary Load, M_{IT} Total Interstitial Load, M_{PT} Total Alveolar Macrophage Load, M_{LN} Lymph Node Load)
Experimental Data Base by Mauderly.[11]

Figure 6: POCK Simulation of Total Pulmonary Retention in Rat Lungs Relative to a Standard Maximum Lung Burden (see text) after Lifetime Exposure (730 days) to Diesel Exhaust between 1 and 1460 $\mu g/m^3$(730 days);
Experimental Data Base by Mauderly.[11]

Figure 7: POCK Simulation of Total and Subcompartmental Pulmonary Particle Mass Retention in Rat Lungs During Chronic Exposure to Diesel Exhaust at 140 $\mu g/m^3$ for Lifetime (730 days);
(M_{alv} Total Pulmonary Load, M_{IT} Total Interstitial Load, M_{PT} Total Alveolar Macrophage Load, M_{LN} Lymph Node Load, M_{SQ} Load of Sequestered Macrophages)
Experimental Data Base by Mauderly.[11]

Figure 8: POCK Simulation of Total and Subcompartmental Pulmonary Particle Mass Retention in Rat Lungs During Chronic Exposure to Diesel Exhaust at 1460 $\mu g/m^3$ for Lifetime (730 days);
(M_{alv} Total Pulmonary Load, M_{IT} Total Interstitial Load, M_{PT} Total Alveolar

Macrophage Load, M_{LN} Lymph Node Load, M_{SQ} Load of Sequestered Macrophages)
Experimental Data Base by Mauderly.[11]

Figure 9: POCK Simulation of Particle Mass Burdens of the Macrophage Pool in Rat Lungs Chronically Exposed to Diesel Exhaust Between 1 and 1460 $\mu g/m^3$ for Lifetime (730 days);
Experimental Data Base by Mauderly[11

Figure 10: Dose-Response Relationships for Different Rat Strains in Lifetime Exposure Studies with Diesel Exhaust or Carbon Black in Terms of Lifetime Tumor Incidence *vs.* Relative Dose, $\mathcal{D}_{rel}\,(t_{end})$
Experimental Data Base for Male and Female Fischer 344 and Fischer 344/N Rats: Mauderly *et al.*[11,15]; for Female Wistar Rats: Heinrich *et al.*[16]

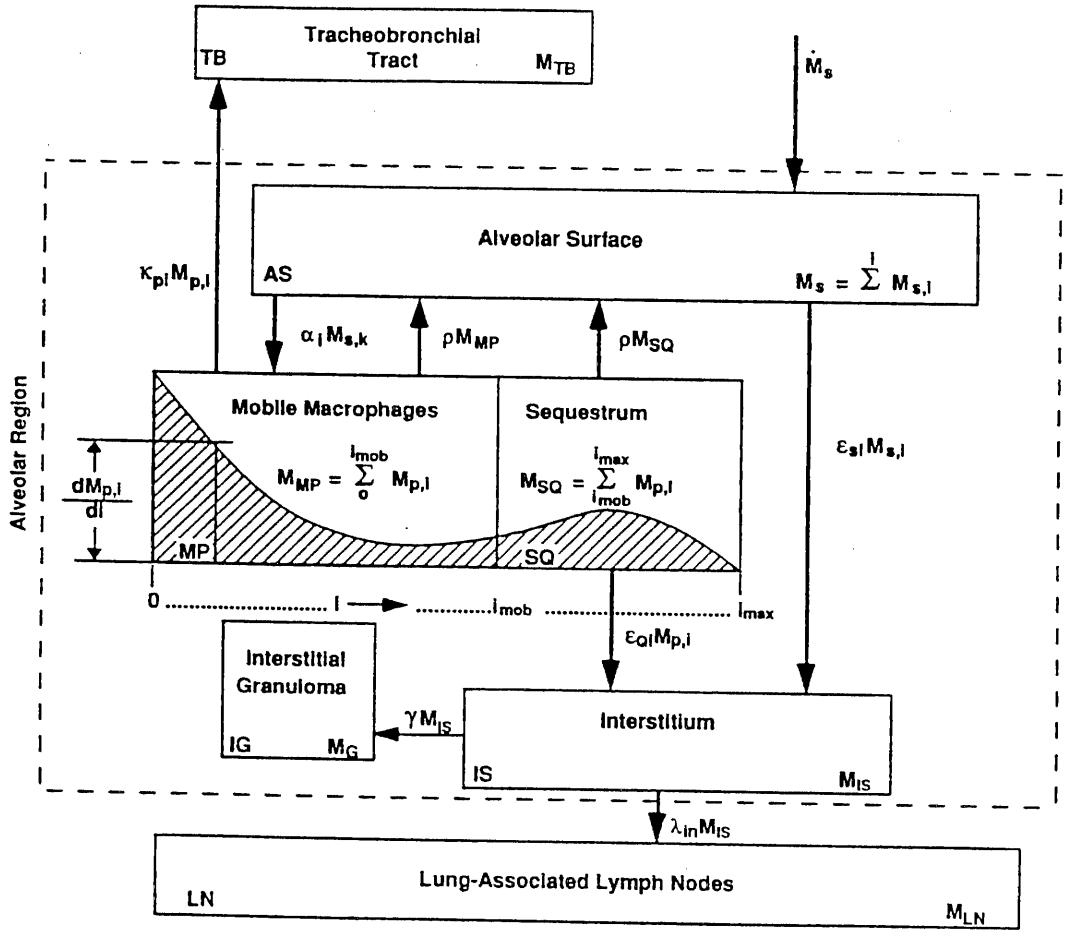
Figure 11: Dose-Response Relationships for Different Rat Strains in Lifetime Exposure Studies with Diesel Exhaust and Carbon Black in Terms of Lifetime Probability of Lung Tumor Incidence, $F(c)$, *vs.* Logarithm of Relative Lifetime Dose, $\mathcal{D}_{rel}\,(t_{end})$, in a Probability Grid.

Figure 12: Time Pattern of the Ratio of Effective Relative Dose (Time-Integrated Interstitial Retention) to Maximally Possible Dose ($D_{ep} \times \frac{t^2}{2}$) for Chronic Exposures to Diesel Exhaust Between 1 and 140 $\mu g/m^3$ during Lifetime (730 days);
Experimental Data Base by Mauderly.[11]

Figure 13: Time Pattern of the Ratio of Effective Relative Dose (Time-Integrated Interstitial Retention) to Maximally Possible Dose ($D_{ep} \times \frac{t^2}{2}$) for Chronic Exposures to Diesel Exhaust Between 140 and 1460 $\mu g/m^3$ During Lifetime (730 days); Experimental Data Base by Mauderly.[11]

Figure 14: Time Pattern of the Ratio of Effective Relative Dose (Time-Integrated Interstitial Retention) to Deposition Rate (D_{ep}) for Chronic Exposures to Diesel Exhaust Between 1 and 140 $\mu g/m^3$ During Lifetime (730 days); Experimental Data Base by Mauderly.[11]

Figure 15: Function $Q(t)$ of the Time Pattern of the Ratio of Effective Relative Dose Rate (Accumulated Interstitial Retention) to Deposition Rate, D_{ep}, for Chronic Exposures to Diesel Exhaust Between 1 and 140 $\mu g/m^3$ During Lifetime (730 days); Experimental Data Base by Mauderly.[11]


Tracheobronchial Tract
TB
M_{TB}
$\dot{M}_s$
Alveolar Surface
AS
$M_s = \sum_{0}^{I} M_{s,I}$
$\kappa_{pI} M_{p,I}$
$\alpha_I M_{s,k}$
ρM_{MP}
ρM_{SQ}
Alveolar Region
Mobile Macrophages
Sequestrum
$M_{MP} = \sum_{0}^{I_{mob}} M_{p,I}$
$M_{SQ} = \sum_{I_{mob}}^{I_{max}} M_{p,I}$
$\varepsilon_{sI} M_{s,I}$
$\frac{dM_{p,I}}{dI}$
MP
SQ
0 ..... I ..... I_{mob} ..... I_{max}
$\varepsilon_{QI} M_{p,I}$
Interstitial Granuloma
IG
M_G
γM_{IS}
Interstitium
IS
M_{IS}
$\lambda_{ln} M_{IS}$
Lung-Associated Lymph Nodes
LN
M_{LN}

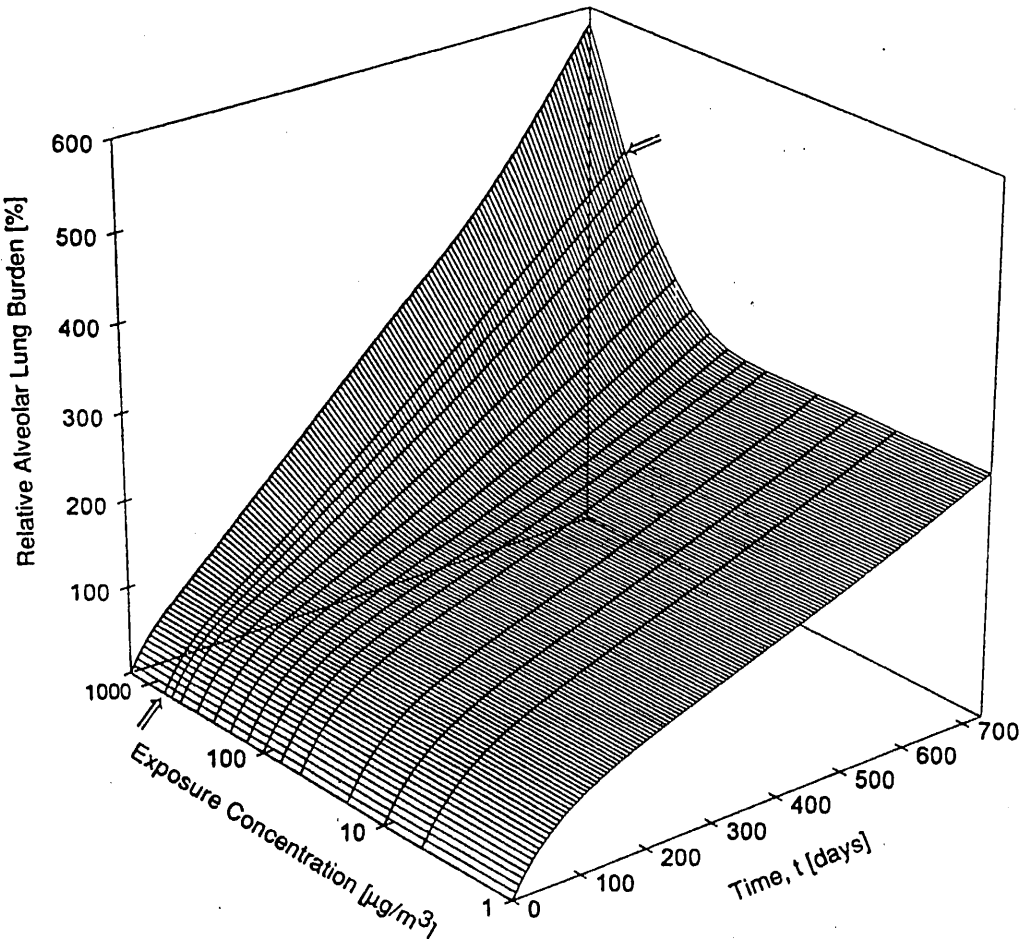

Relative Alveolar Lung Burden [%]
600
500
400
300
200
100
1000
100
10
1
Exposure Concentration [µg/m3]
0
100
200
300
400
500
600
700
Time, t [days]

Fig. 4

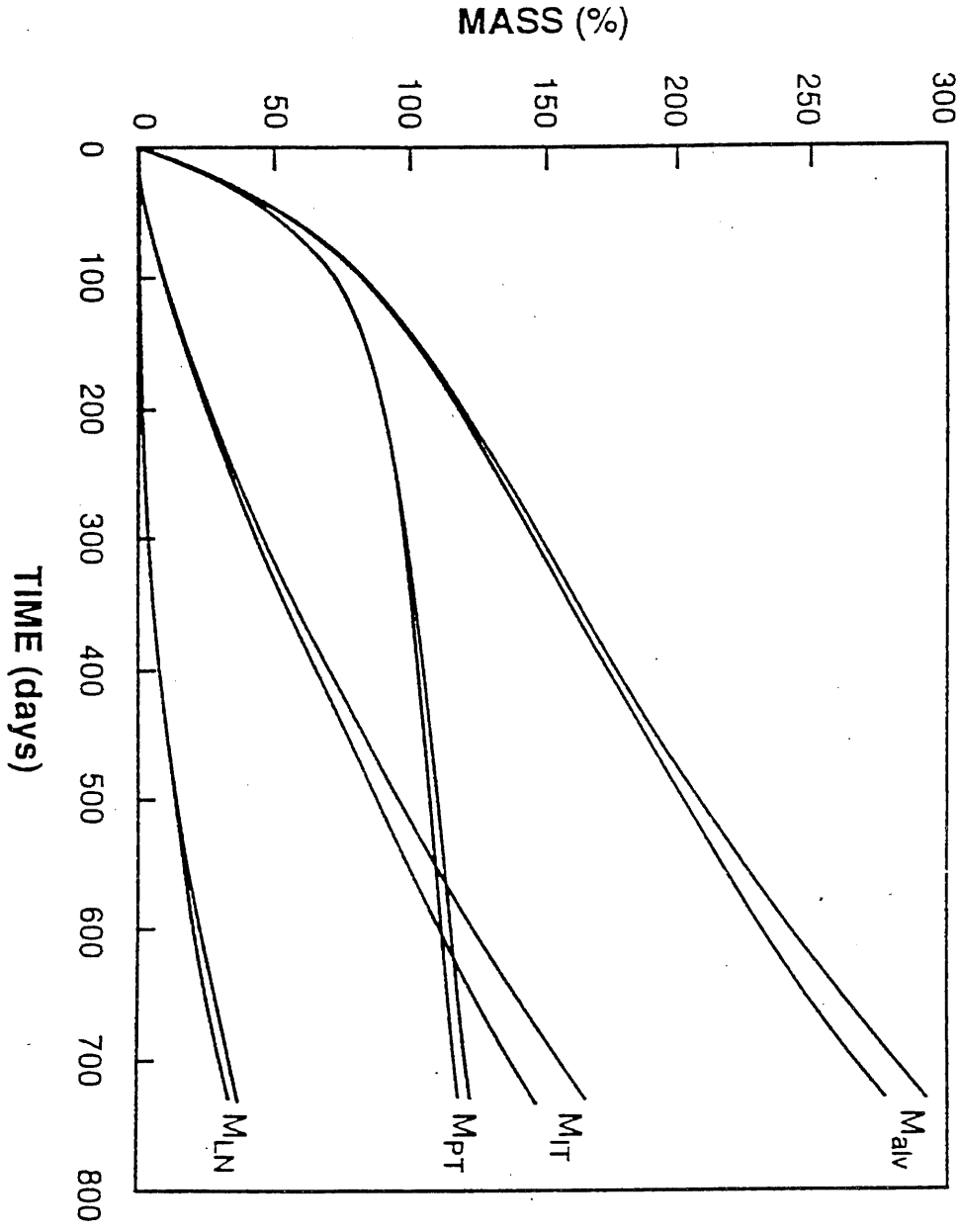

MASS (%)
0
50
100
150
200
250
300
TIME (days)
0
100
200
300
400
500
600
700
800
M_{LN}
M_{PT}
M_{IT}
M_{alv}

Fig. 5

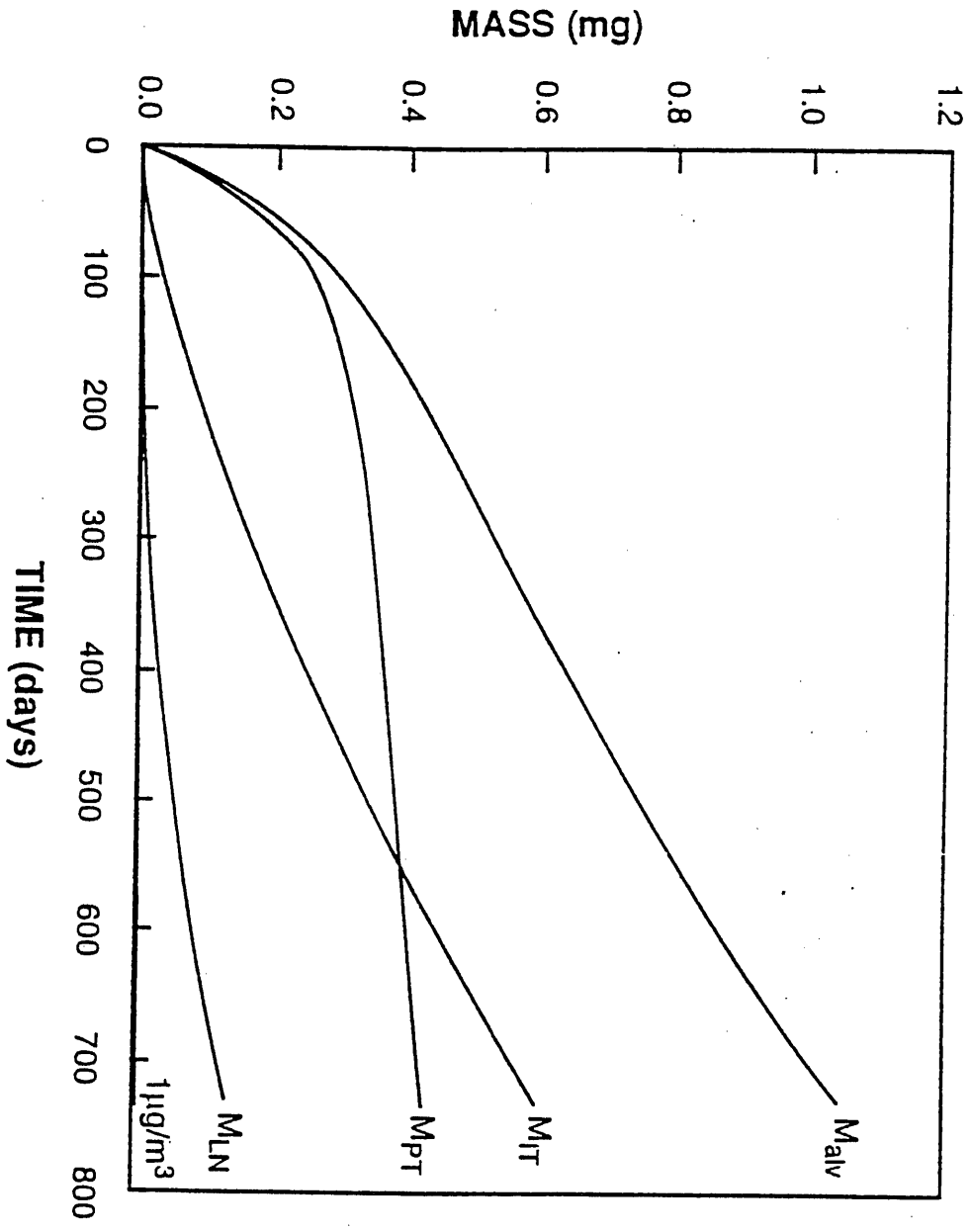
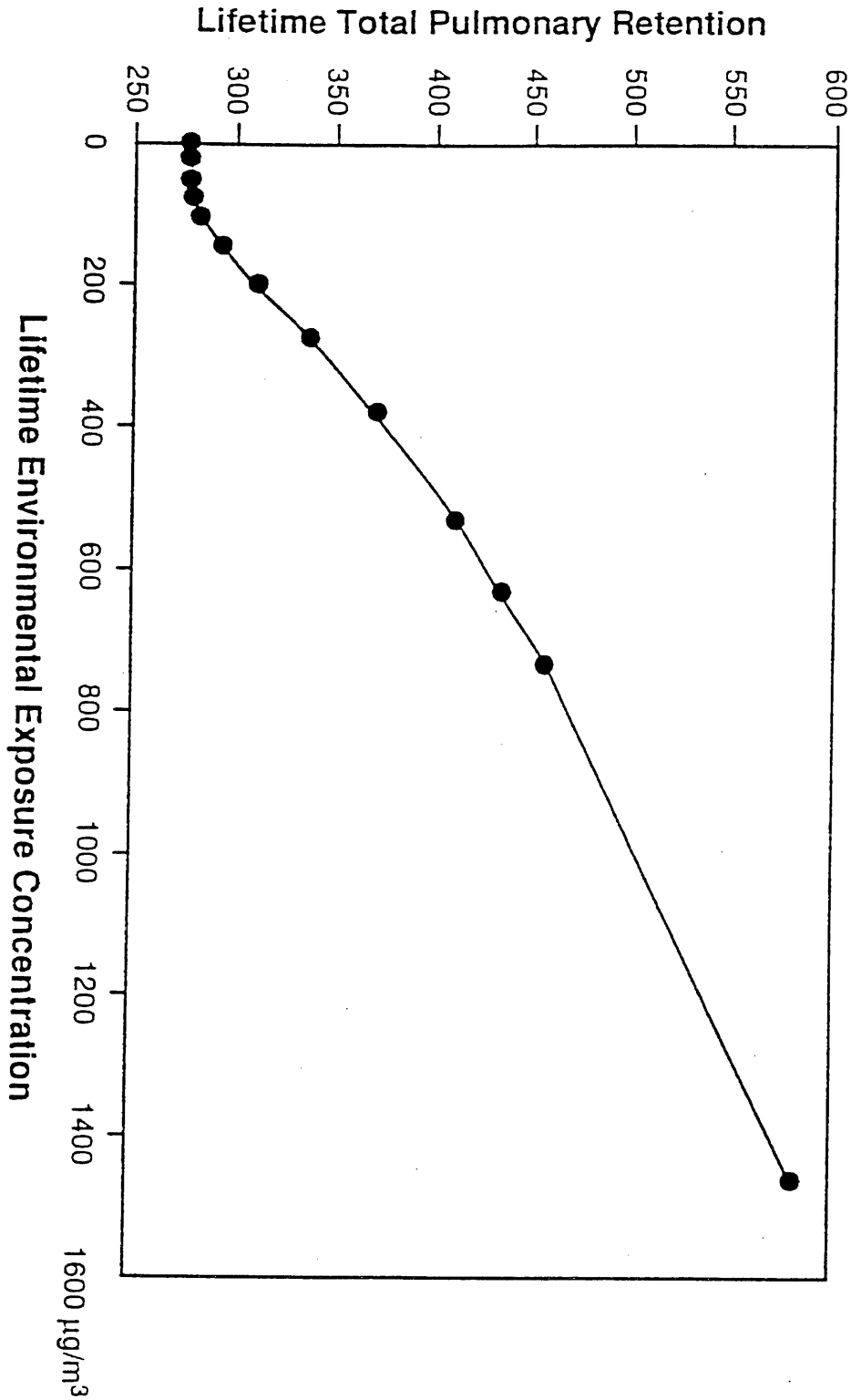

MASS (mg)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
TIME (days)
0
100
200
300
400
500
600
700
800
M_{alv}
M_{IT}
M_{PT}
M_{LN}
1µg/m³

Fig. 6


Lifetime Total Pulmonary Retention
250
300
350
400
450
500
550
600
0
200
400
600
800
1000
1200
1400
1600 µg/m3
Lifetime Environmental Exposure Concentration

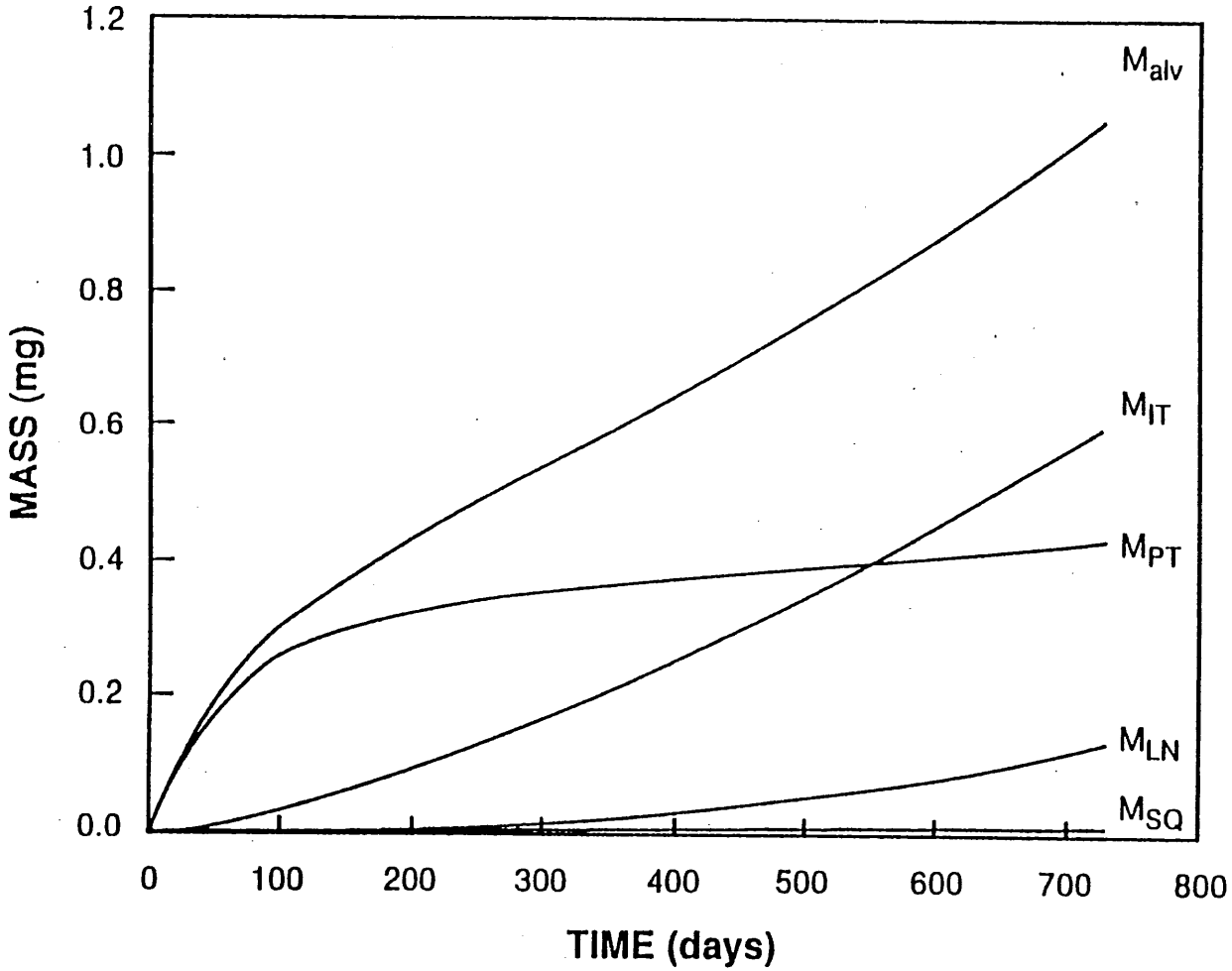

1.2
1.0
0.8
0.6
0.4
0.2
0.0
MASS (mg)
0
100
200
300
400
500
600
700
800
TIME (days)
M_{alv}
M_{IT}
M_{PT}
M_{LN}
M_{SQ}

Fig. 7

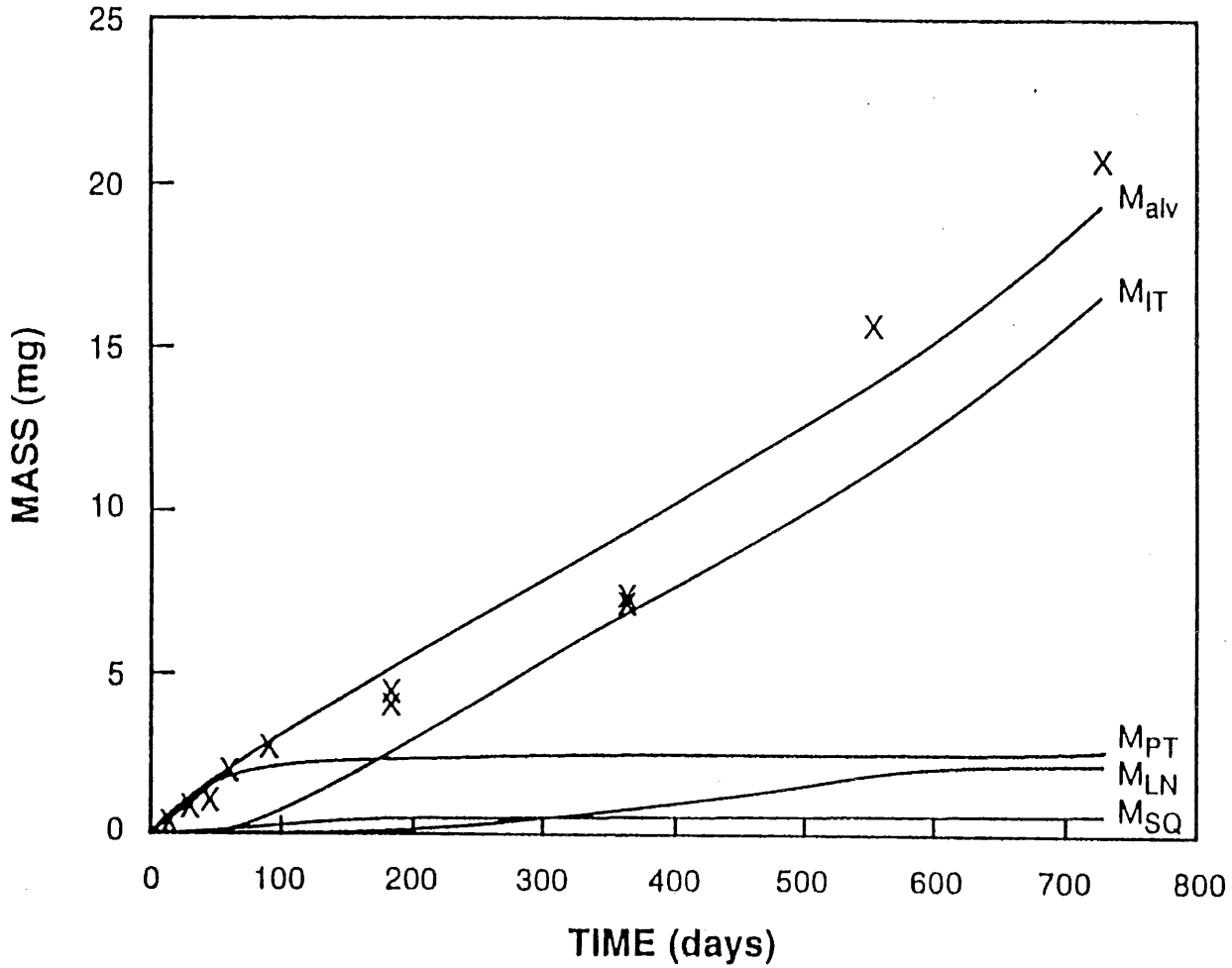
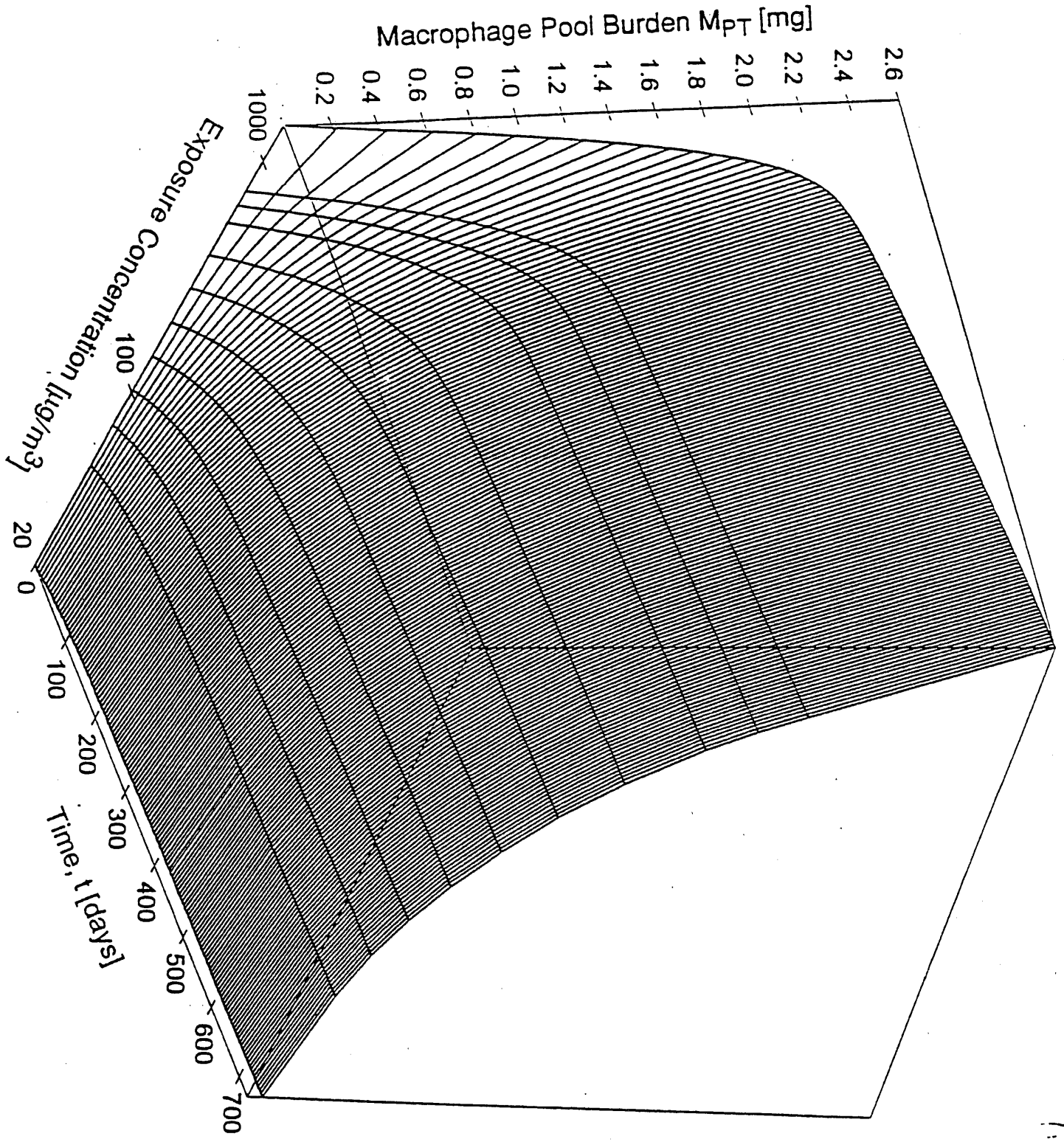
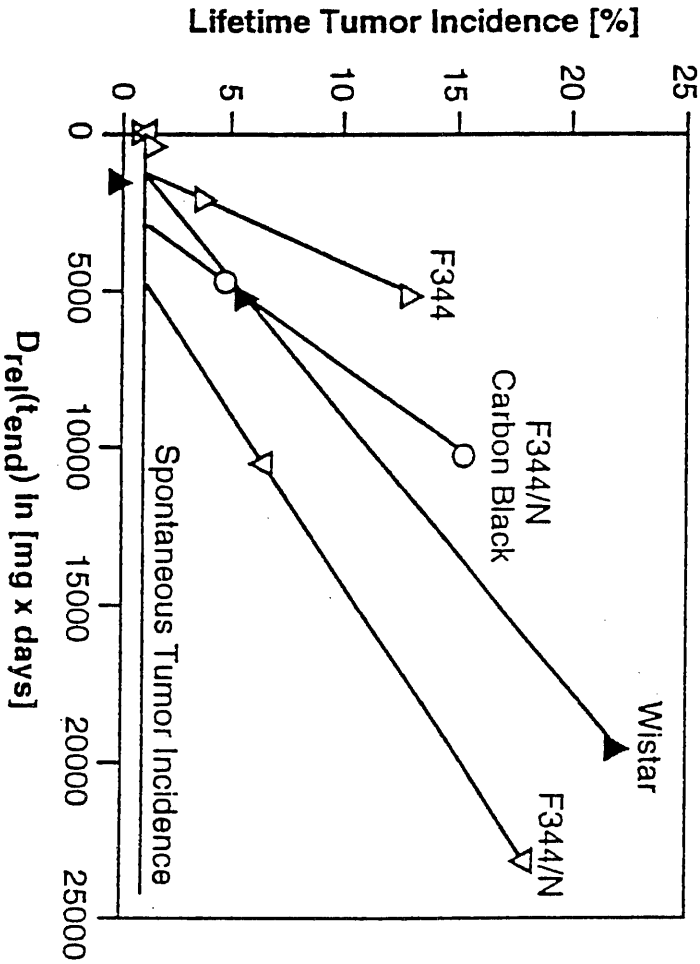
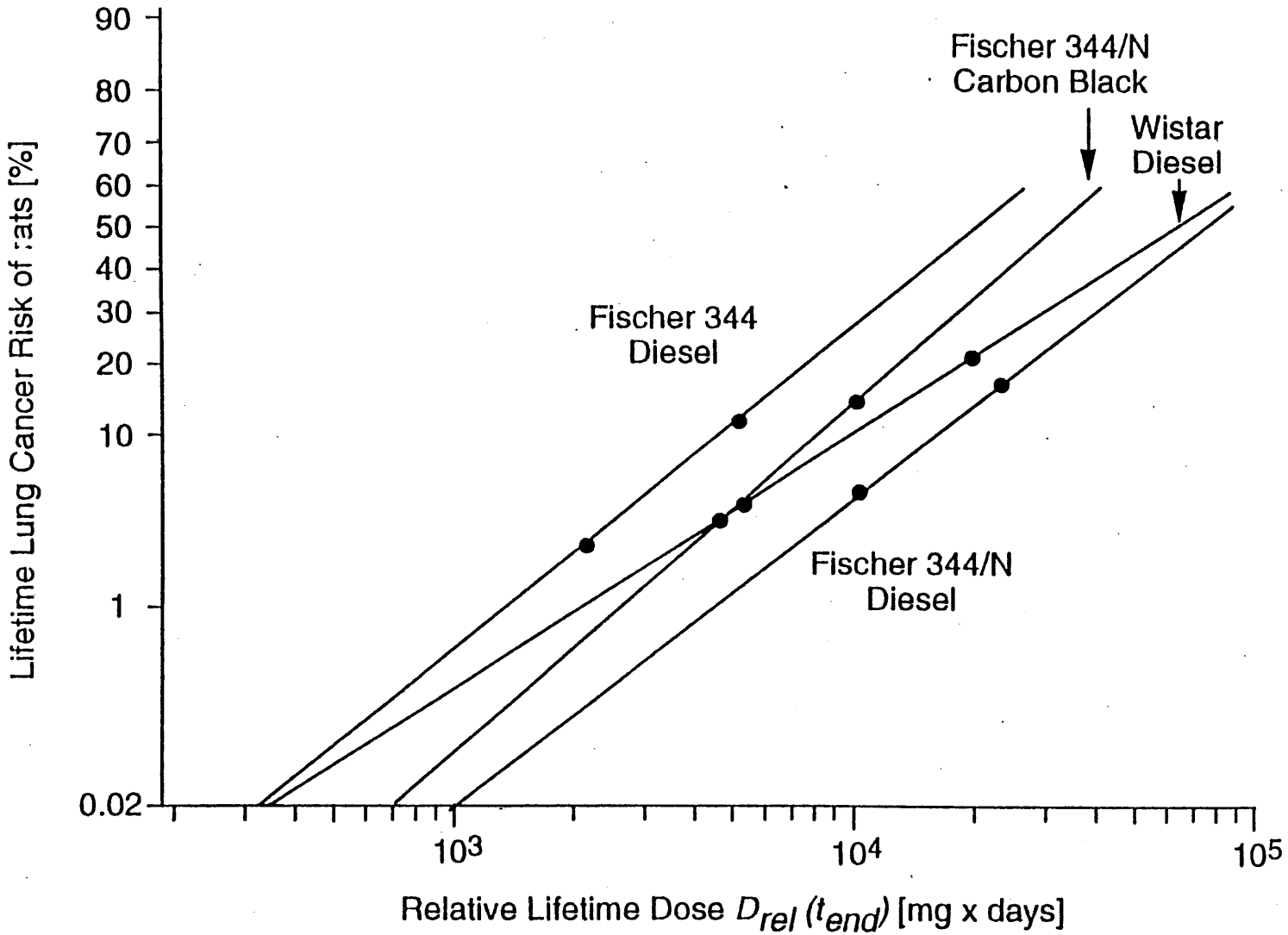

25
20
15
10
5
0
MASS (mg)
0
100
200
300
400
500
600
700
800
TIME (days)
M_{alv}
M_{IT}
M_{PT}
M_{LN}
M_{SQ}

Fig.8


Macrophage Pool Burden M_{PT} [mg]
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
Exposure Concentration [µg/m3]
1000
100
20
0
Time, t [days]
100
200
300
400
500
600
700


Lifetime Tumor Incidence [%]
0
5
10
15
20
25
0
5000
10000
15000
20000
25000
$D_{rel}(t_{end})$ ln [mg x days]
F344
F344/N Carbon Black
Wistar
F344/N
Spontaneous Tumor Incidence


Lifetime Lung Cancer Risk of rats [%]
90
80
70
60
50
40
30
20
10
1
0.02
Fischer 344/N
Carbon Black
Wistar
Diesel
Fischer 344
Diesel
Fischer 344/N
Diesel
10³
10⁴
10⁵
Relative Lifetime Dose D_{rel} (t_{end}) [mg x days]

4-568

Fig. 27

Fig. 12

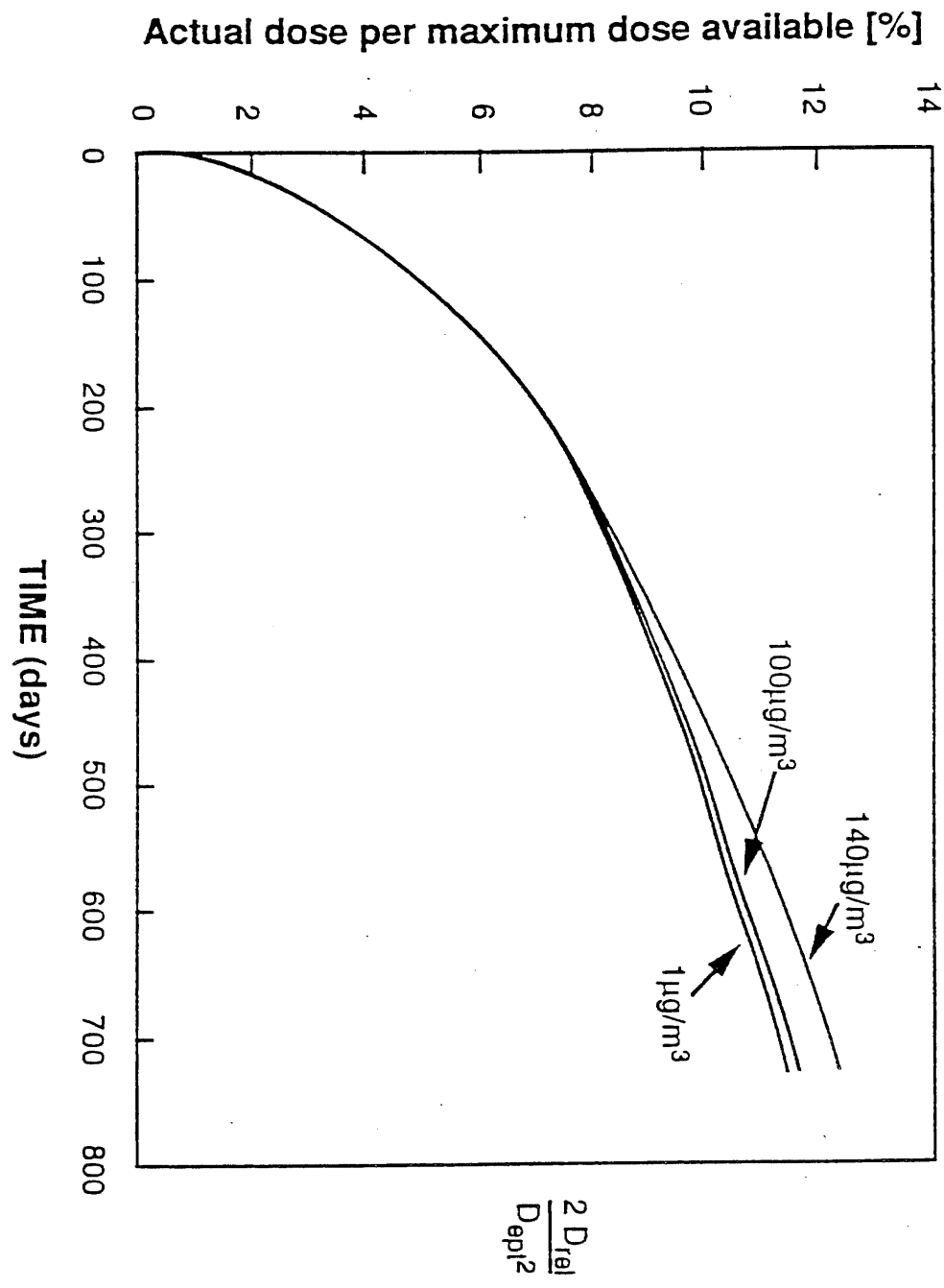

Actual dose per maximum dose available [%]
0
2
4
6
8
10
12
14
0
100
200
300
400
500
600
700
800
TIME (days)
100µg/m3
140µg/m3
1µg/m3
2 Drel / Depl2

Fig. 16

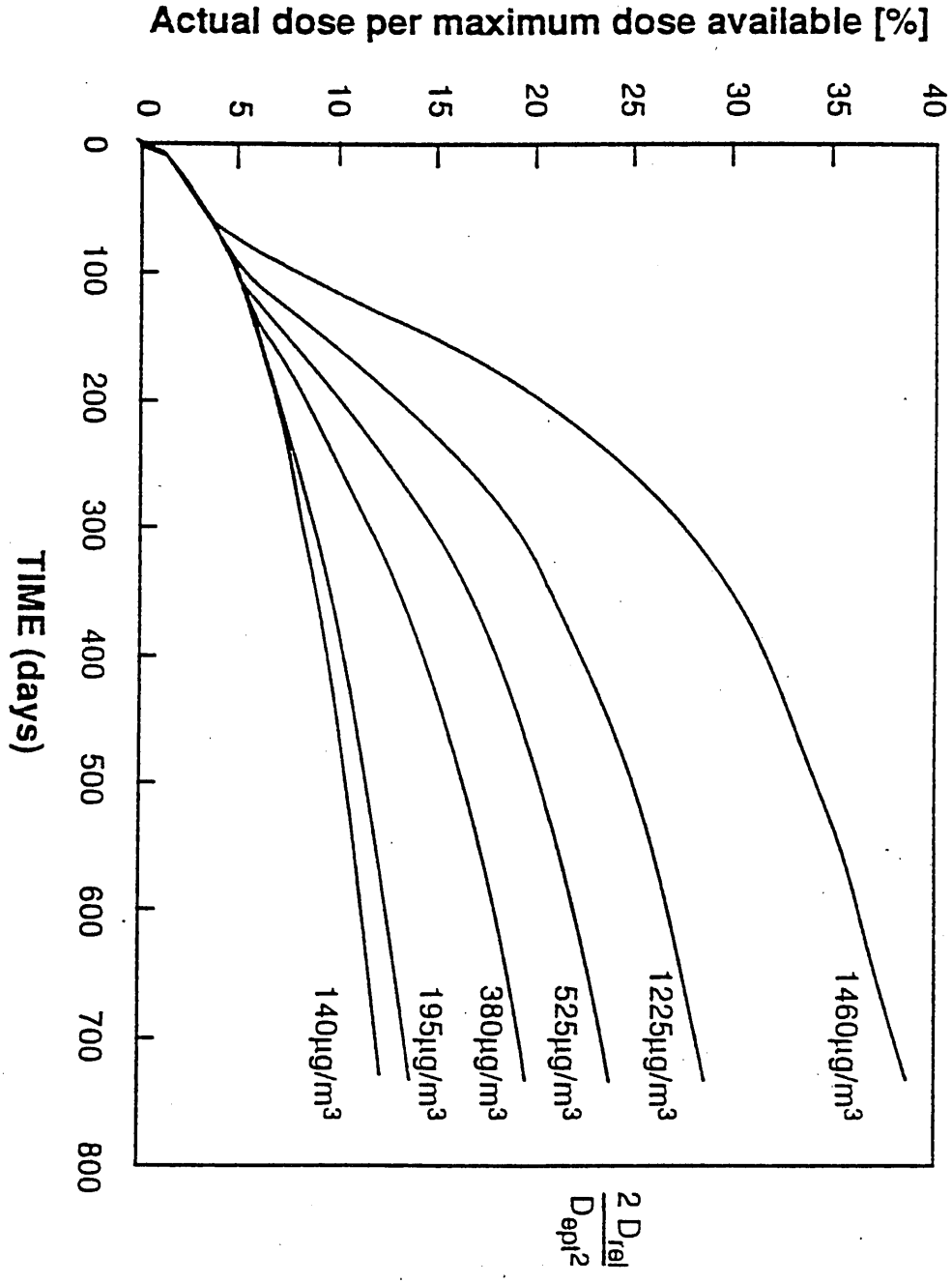
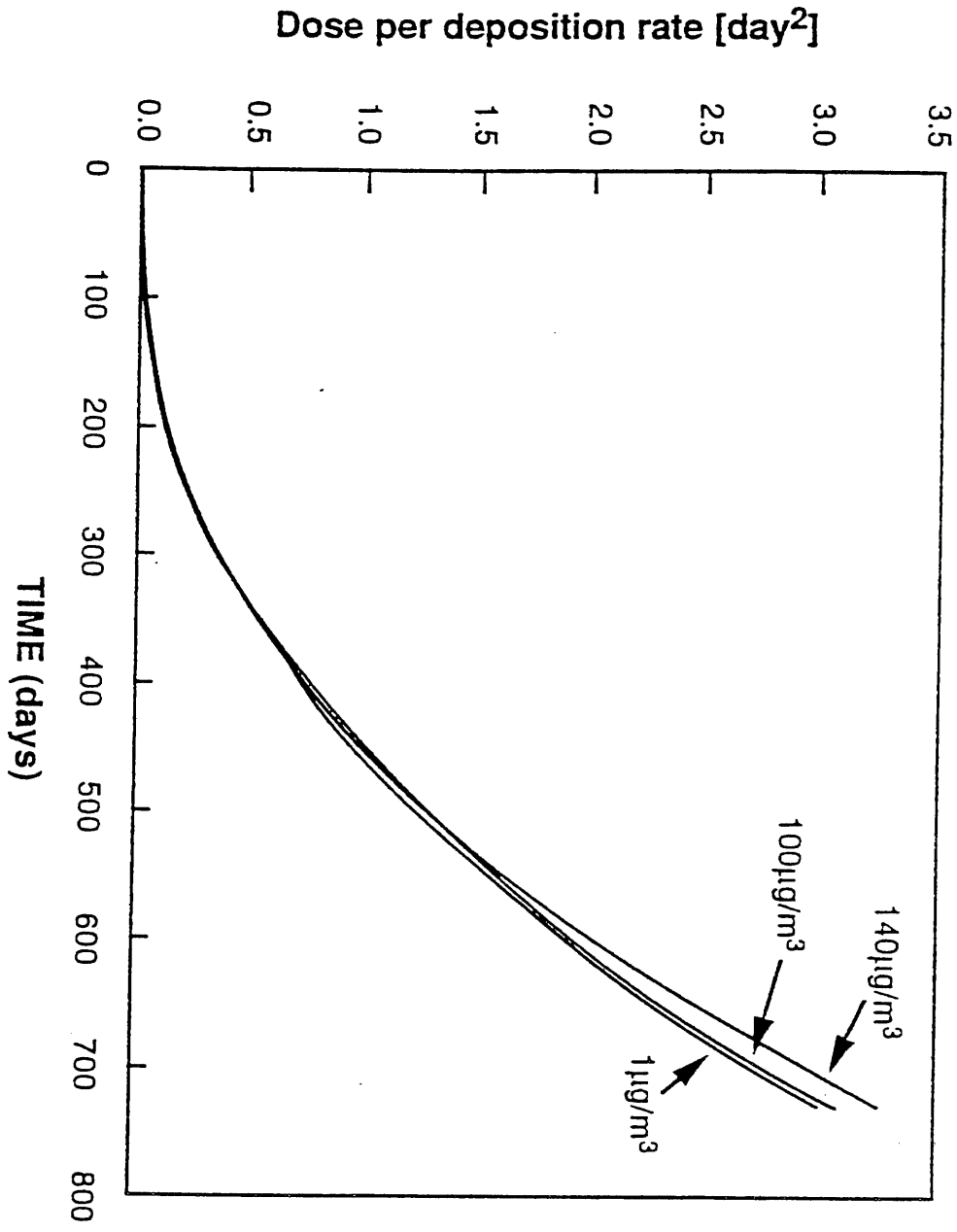
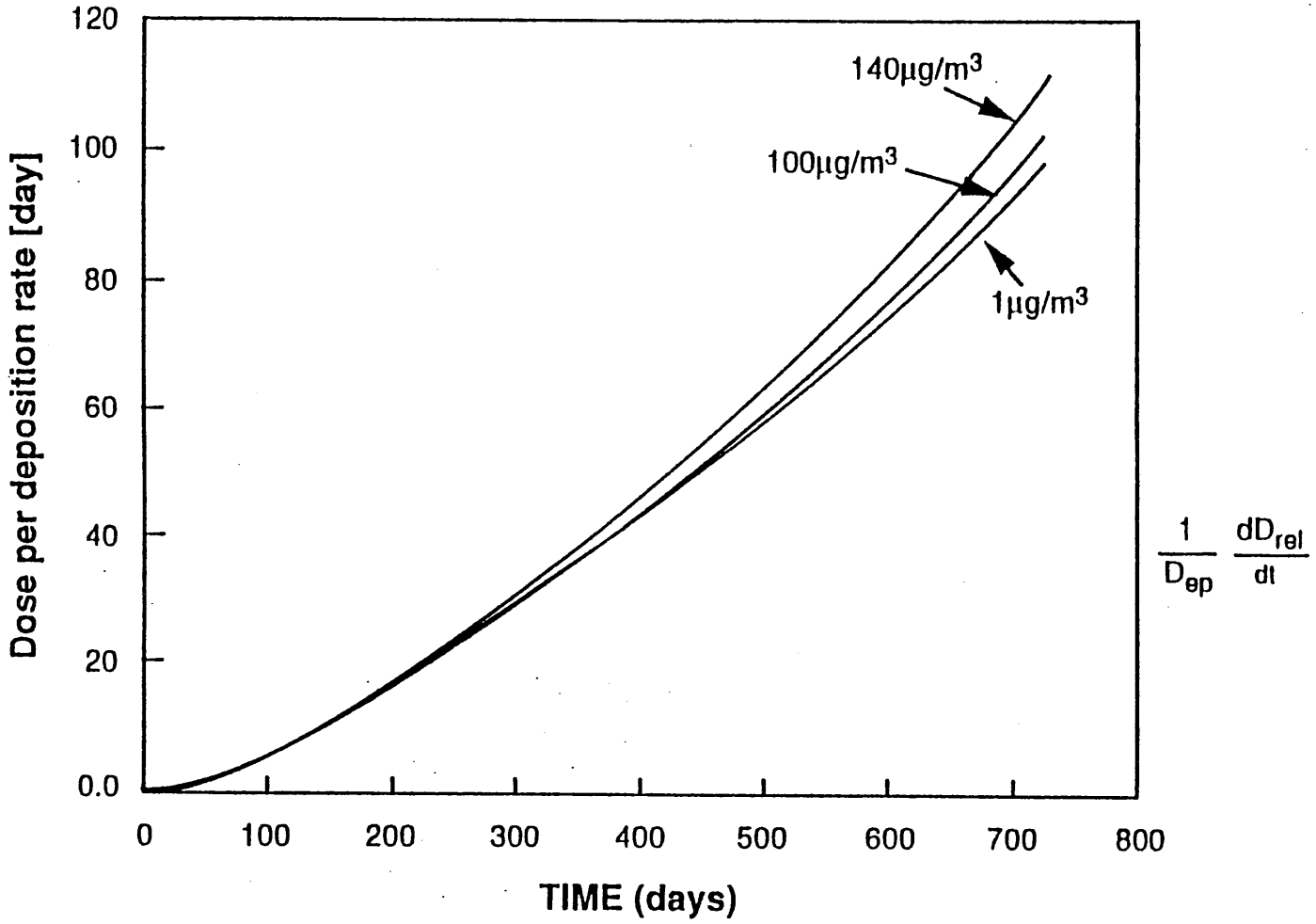

Actual dose per maximum dose available [%]
0
5
10
15
20
25
30
35
40
TIME (days)
0
100
200
300
400
500
600
700
800
1460µg/m3
1225µg/m3
525µg/m3
380µg/m3
195µg/m3
140µg/m3
2 D_rel / D_epl2

Fig. 9.11


Dose per deposition rate [day2]
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
0
100
200
300
400
500
600
700
800
TIME (days)
140µg/m3
100µg/m3
1µg/m3


120
100
80
60
40
20
0.0
0
100
200
300
400
500
600
700
800
140µg/m3
100µg/m3
1µg/m3
Dose per deposition rate [day]
TIME (days)
1/Dep dDrel/dt

Alternative Hypotheses Linking Outdoor Particulate Matter (PM) with Daily Morbidity and Mortality

Peter A. Valberg and Ann Y. Watson

Gradient Corporation, 44 Brattle Street, Cambridge, MA 02138

and

Harvard School of Public Health, Boston, MA 02115

Correspondence: Dr. Peter A. Valberg
Gradient Corporation
44 Brattle Street
Cambridge, MA 02138
(617) 576-1555

ABSTRACT

It has not been possible to causally link outdoor PM with changes in daily morbidity/mortality because of our inability to identify a toxic agent that is consistent across all the epidemiologic studies, and that has been validated by laboratory toxicology. An alternative explanation is possible: Varying levels of ambient PM may be correlated to conditions that directly modify morbidity/mortality rates or promote the production of, and increase people's exposure to, lung toxins. That is, the same changes in weather and human behavior that give rise to "day-to-day fluctuations in ambient particulate matter" can also give rise to changes in physiologic factors, such as stress, and in exposures, such as to indoor air. PM levels may thus only be a marker for other, causal factors. Weather fluctuations leading to cold stress or heat stress result in an increasing fraction of time spent indoors. Moreover, inclement weather promotes the use of climate-control systems, which can generate increased indoor levels of potentially toxic airborne particles. At the same time, weather stress tends to increase outdoor PM levels because of the increased use of vehicles and an increased demand for electric power for heating or air conditioning. Therefore, personal exposure to indoor toxins, may be linked to outdoor PM concentrations. The major significance of indoor air contaminants is that, unlike outdoor PM, toxicological and epidemiological studies of indoor air support the biological plausibility of morbidity and mortality risk for indoor allergens, bioaerosols, and perhaps environmental tobacco smoke (ETS). In evaluating causality in the epidemiologic studies, one must consider the factors that drive outdoor PM fluctuations in the first place to determine if the observed morbidity/mortality changes can be caused by pathways other than the hypothetical frank toxicity from inhalation of ambient PM.

KEY WORDS: inhalation toxicology, PM_{10}, respirable particles, confounding factors, ambient aerosols, causality

INTRODUCTION

Recent US epidemiologic studies showing health effects from ambient particulate matter (PM) have come under close scrutiny [1-5]. These studies report small changes in daily mortality [6-11] that were associated with fluctuations in levels of outdoor PM. For the general population, the USEPA [5] estimated that for every 50 $\mu g/m^3$ PM_{10} increment, an excess of 2.5% to 5% deaths might occur. Elderly individuals with pre-existing respiratory or cardiovascular disease appear to be at greater risk [5,9,12-14]. Effects on morbidity [15] also have been associated with fluctuations in ambient PM. However, it has not been possible to causally link outdoor PM with changes in daily morbidity/mortality because of an inability to identify a toxic agent that is consistent across all the epidemiologic studies, and that has been validated by laboratory toxicology [16]. In this paper, we present an alternative interpretation of the epidemiologic studies and discuss how indoor-air pollutants may confound the observed association between outdoor PM and health effects. We also summarize some provocative data that we feel highlights the need for further systematic investigation of our hypothesis; however, it is not our purpose to provide an in-depth review of the literature on indoor-air quality.

ALTERNATIVE INTERPRETATIONS: OUTDOOR PM IS A SURROGATE VARIABLE

When evaluating the epidemiologic results, one needs to ask *"Why are there day-to-day fluctuations in PM?"*, and, *"Will not the same factors that cause such fluctuations in PM also signal changes in human behavior and exposure, which may be causally linked to morbidity and mortality?"* Figure 1 illustrates that varying levels of ambient PM can be correlated to conditions that may directly modify morbidity/mortality rates or promote the production of, and increase people's exposure to, lung toxins. That is, the same changes in weather and human behavior that give rise to fluctuations in ambient PM can also modify exposures, such as to indoor air contaminants, and physiologic factors, such as stress. Weather fluctuations leading to cold stress or heat stress result in an increasing fraction of time spent indoors. Moreover, inclement weather promotes the use of climate-control systems, which can generate increased indoor levels of potentially toxic airborne particles. At the same time, weather extremes tend to increase outdoor PM levels because of the increased use of vehicles and an increased demand for electric power for heating or air conditioning. An increase in centrally monitored ambient PM levels would be but a marker for these weather changes and/or for alterations in human-activity patterns. Thus, it is important to consider the factors that drive outdoor PM fluctuations in the first place to determine if the observed morbidity/mortality changes can be caused by pathways other than the hypothetical toxicity attributed to inhalation of low-level, ambient PM. Evaluation of whether the epidemiologic results point to a causal link should consider human-activity patterns and their impact on exposure. Furthermore, any link thought to be causal should be supported by biological plausibility.

Kalkstein and his collaborators have defined "synoptic" categories of weather and have shown clear effects of weather patters on health. [17] Seasonality explains a significant amount of variability in mortality. Investigators supported by the Health Effects Institute attempted to determine how "oppressive" weather conditions interacted with PM effects, and they found a mortality response to PM even when "oppressive" days were excluded. However, when days of similar PM concentration were grouped together, mortality response was sensitive only to variations in meteorology. [18] Thus, the analyses that have been done thus far have established that weather patterns appear to have a direct effect on human health, and hence it becomes difficult to assure that inclement meteorological conditions can be removed as confounding factors from the reported PM associations. The Kalkstein categories are chosen to cluster similar weather days, but not to optimally predict mortality. Little attention has been paid to selecting a physiologically based combination of weather patterns that might maximally perturb homeostasis.

We have chosen to discuss indoor-air quality to illustrate the potential for alternative pathways of causation that may confound the linkage between ambient PM and increased mortality/morbidity. People spend the majority of their time indoors; therefore, indoor PM contributes a significant fraction to total personal exposure. In addition, toxicologic and epidemiologic studies of indoor air, unlike the case of outdoor PM, support the biological plausibility of morbidity/mortality risk from indoor allergens, bioaerosols, and perhaps environmental tobacco smoke (ETS).

INDOOR-AIR EXPOSURES

Time-activity analyses indicate that Americans spend the majority of their time indoors. Robinson and Nelson (1995) reported that an average resident spends approximately 21 hours indoors (87.2%), 100 minutes in (or near) a vehicle (7.2%), and 80 minutes outdoors (5.6%). [19] Estimates by Spengler and Sexton (1983) suggest that Americans spend closer to 93% of their time indoors and only 2% of their time outdoors. [20] Elderly individuals with pre-existing respiratory or cardiovascular are considered to be at greater risk from exposure to PM. Therefore, it is important to consider the likely exposure scenario for this population. It is probable that an elderly population, especially persons that are infirm, would spend an even greater fraction of their day indoors, particularly in the event of inclement weather and/or air pollution episodes. The presence of airborne particulate or haze coupled with inclement weather conditions (*e.g.*, uncomfortably high or low temperatures, high humidity, low barometric pressures, wind chill) drives the population, especially compromised individuals, indoors. Once indoors the operation of climate control systems (consequent to the inclement weather) increases the exposure to indoor aerosols. Although outdoor particulate can partially penetrate indoors, the indoor environment is the major exposure category, and indoor aerosol sources represent a significant exposure variable.

It should be noted that in many of the PM epidemiologic studies, outdoor levels of PM were measured using a single central monitor, often at a considerable distance from the subject population. Because the epidemiologic studies are population-based, we do not have personal exposure information on the potentially susceptible subpopulations. While factors like PM exposures during commuting and work may be important for the general population, these microenvironments are probably not relevant for the elderly or infirm. The home or a health care facility is where these people spend the majority of their time, and careful comparisons are needed between these indoor environments (and their unique aerosol sources) and ambient pollutant measurements.

Three large-scale studies have characterized the levels and sources of indoor PM (reviewed in 1996 by Wallace [21]): (1) the Harvard Six-City study, (2) the New York State ERDA study, and (3) the EPA Particle Total Exposure Assessment Methodology (PTEAM) study. After reviewing these studies and several smaller-scale studies, Wallace noted the following:

- When outdoor concentrations of fine PM were low, mean-indoor levels were as much as two-fold higher than outdoor levels.

- Using a mass-balance model, authors of the EPA PTEAM study estimated that outdoor air contributed 75% of the $PM_{2.5}$ and 67% of the PM_{10} particles in average Riverside homes. However, Riverside has among the highest outdoor PM levels in the U.S. (annual mean PM_{10} of 66 $\mu g/m^3$ in 1994, with a 24-hr maximum of 184 $\mu g/m^3$) and a warm, dry climate; if residents kept their windows open, one would expect a high penetration of outdoor particulate. These estimates apply only to Riverside, and data from other two major studies indicate that outdoor penetration of particulate accounted for less than half of the total indoor particulate.

- Cigarette smoking was the largest source of indoor particulate for those homes with smokers, adding 25-45 $\mu g/m^3$ of fine particles. Cooking represented the second largest indoor source.

- Data from the EPA PTEAM study suggest that the source of as much as 25% of the indoor $PM_{2.5}$ and PM_{10} was not known (that is, sources other than smoking, other combustion sources, cooking, dusting, vacuuming, spraying, or cleaning)

- Personal PM exposures were higher (from 50%-100%) than either outdoor or indoor PM values and were often not correlated with outdoor concentrations.

- High personal exposures were attributed to a "personal cloud" effect. Although not completely understood, re-entrainment of household dust and localized sources of particles have been suggested as sources for the "personal cloud" effect.

Wallace also presented some results that emphasize the importance of PM derived from indoor sources.

- Seasonal effects on indoor PM levels were observed in some studies; levels in the winter were generally higher than in the summer, and the impact of smoking was greater during the winter (Spengler *et al.*, 1987; Quackenboss *et al.*, 1991, cited in [21]).

- Kerosene heater use contributed about 15 $\mu g/m^3$ to indoor PM in one of the counties evaluated in the New York State ERDA study; in the other country evaluated, an additional contribution of kerosene heaters to PM could not be detected.

- At night, the use of woodburning stoves increased ambient and indoor levels of $PM_{2.5}$ approximately 50% (Highsmith *et al.*, 1988 and 1991, cited in [21]).

- In residences with smokers, indoor levels of respirable particulate (RSP) were significantly higher in homes with central air conditioning (114 $\mu g/m^3$) than in homes without air conditioning (52 $\mu g/m^3$) (Morandi *et al.*, 1986, cited in [21]).

- Although mean levels of PM_{10} were not significantly increased with the use of kerosene heaters [73.7 $\pm$ 7.3 (SE) $\mu g/m^3$ *versus* 56.1 $\pm$ 5.7 $\mu g/m^3$] in eight mobile homes, two of the mobile homes experienced increases as high as 112 and 113 $\mu g/m^3$ when the heaters were on (Mumford *et al.*, 1991, cited in [21]).

- The use of a portable ultrasonic humidifier located in a kitchen, resulted in bedroom $PM_{2.5}$ levels of 593 $\mu g/m^3$ (when using tap water) or 27 $\mu g/m^3$ (when using distilled water); background levels were 11 $\mu g/m^3$. Use of a humidifier for less than 0.5 hour in a closed bedroom resulted in a one-hour average concentration of 6,300 $\mu g/m^3$ (Highsmith *et al.*, 1988, cited in [21]).

These examples demonstrate that human behavior and the use of climate-control system influence indoor PM concentrations, and consequently, PM dose from indoor sources.

In summary, people spend the majority of their time indoors breathing PM that may not be well characterized either quantitatively or qualitatively by outdoor monitors. Not only are mean PM exposures higher indoors than outdoors, but under certain circumstances, peak levels of indoor PM can be very high. In addition, personal PM exposures are often higher than reflected by either outdoor or indoor

concentrations. Finally, indoor exposures involve many components (*e.g.*, bioaerosols, cooking particles, ETS, allergens) that are not present in outdoor PM, and moreover, these exposures are elevated by the use of climate control systems.

INDOOR-AIR CONTAMINANTS

Two specific components of indoor air may confound assigning a causal role to ambient PM: ETS and bioaerosols. Each of these two components has a different influence on the interpretation of PM epidemiologic data. Environmental tobacco smoke indoors is not measured by stationary outdoor monitors; thus, particle exposure of the target population residing with smokers would be underestimated and mischaracterized. For example, day-by-day ETS exposure indoors may vary because inclement weather could result in a greater fraction of cigarettes smoked being smoked indoors.

Bioaerosols derive primarily from indoor sources, are known to adversely affect respiratory function, and can do so at ambient concentrations. Indoor levels of bioaerosols may increase as a result of using various climate-control systems. Under inclement climatic conditions, which in turn may be correlated with high ambient PM levels, persons utilize climate-control systems, such as air conditioning, portable fans, or heat sources. Climate-control systems can affect the indoor air quality by increasing the burden of indoor particulate in general, and biological aerosols, specifically.

Environmental Tobacco Smoke

One important aspect of indoor air not recorded with stationary outdoor monitors is exposure to ETS. As noted above, cigarette smoke is the largest indoor source of fine particulate in those homes with a smoking resident. The impact of smoking on indoor-air quality range from 25 to 47 $\mu g/m^3$, and of a single cigarette from 1 to 2 $\mu g/m^3$ for a 24-hour period [21]. Twenty-five to 47 $\mu g/m^3$ represents a significant PM exposure, especially when the mean outdoor PM concentrations under study range from about 20 to 80 $\mu g/m^3$. Given that (1) ETS represents a significant PM exposure, (2) people spend the majority of their time indoors, (3) 31% of U.S. homes have a smoker (USEPA NHAPS data), and (4) the USEPA (1995) identified current or former smokers as a subpopulations at higher risk [5], the contribution of ETS to personal PM exposure and to daily mortality/morbidity should be considered.

Biological Aerosols

Bioaerosols are airborne substances, either living or derived from living organisms, and include particles, large molecules, or volatile compounds. Viruses, bacteria, fungi, pollen, protozoa, algae, and components of arthropods or mammals can either be present in the air or release spores, toxins, antigens, or volatiles into the air. Bioaerosols are present in both the outdoor and indoor air, but because major sources exist indoors and people spend the majority of their time indoors, we will focus on indoor bioaerosols and those conditions that increase their airborne levels. Table 1 summarizes some of the characteristics and health effects of common bioaerosols [22].

Table 1: Characteristics of Some Common Biological Aerosols

Organism	Bioaerosol	Example	Health Effect
Bacteria	whole	*Legionella*	pneumonia
	spores	*Thermoactinomyces*	HP
Fungus	whole	*Sporobolomyces*	HP
	spores	*Alternaria*	asthma
	spores	*Penicillium*	HP
	antigens	*Alternaria*	asthma, HP
	volatiles	*Penicillium*	irritant
Pollen	spores	ragweed	asthma
Protozoa	antigens	*Acanthmoeba*	HP
Algae	whole	*Chlorococcus*	asthma
Arthropods	feces	mites	asthma
Mammals	scales, feces, saliva, urine	rodents, cats, dogs	asthma

approximate size range is $<0.1\mu m$ to 60 μm; HP = hypersensitivity pneumonitis

Exposure to the various bioaerosols at sufficient concentrations can result in respiratory infectious disease, hypersensitivity diseases, or respiratory-tract irritation [22-24]. Human-transmitted infectious disease will not be considered here, but respiratory infection has an acknowledged variation with weather patterns and season. Some infectious microorganisms, such as *Legionella pneunmophila*, are not dependent on human hosts for survival and can remain viable in environmental reservoirs. Hypersensitivity pneumonitis (allergic alveolitis) is an antigen-mediated, noninfectious pneumonia resulting in potentially permanent lung dysfunction. Its occurrence is associated with contaminated water reservoirs in central ventilation systems or in small spray humidifiers. Bacterial and fungal spores or antigens have been implicated in several hypersensitivity pneumonitis outbreaks. Humidifier fever is characterized by fever, chills, and fatigue, and may be caused by either airborne antigens or toxins. Although asthma and hay fever attacks can be precipitated by outdoor pollens, indoor sources of antigens also exist. Fungal antigens, animal byproducts, and dust mites are notorious antigenic compounds and can elicit asthmatic reactions [25].

Microorganisms may originate either from outdoor or indoor sources. Ventilation (the indoor-outdoor air exchange rate) regulates the relative concentrations between indoor and outdoor biocontaminants. Ventilation rates also affect indoor humidity levels; moreover, air ducts, plenums, and filters can serve as reservoirs for microbiological contamination [21-22]. Indoor exposure to

microorganisms is a function of whether there are locations where microbes can reside and amplify, and whether a means is available by which they can be dispersed into the air.

Indoor moisture is one of the most important factors regulating microbial contamination and growth [22-24]. Therefore, any ventilation system or appliance containing a water reservoir or drip pan may harbor microorganisms. Even porous manmade insulation on the inside of central heating housing surfaces, ventilation, and air-conditioning (HVAC) systems can serve as a source of microorganisms. For example, lower respiratory tract infections have been shown to be increased in children in homes with evaporative cooling [25a].

Water content in the air (relative humidity) is another factor affecting microorganism levels [22-23]. During the summer months, relative humidity is quite high in certain parts of the country, and the interior of homes without dehumidifiers would also experience high humidity. The winterizing of homes and buildings for energy conservation can increase the water content as well as trap indoor-air-generated pollutants. Relative humidity can reach >75% in electrically heated mobile and modular homes designed for maximal energy efficiency [22]. Therefore, the relative humidity indoors is a function of climate, building construction, and climate-control systems. The WHO [23] has cautioned that the incidence of upper respiratory illness might increase in people suffering from asthma and allergies if relative humidity exceeds 65%. The WHO also concluded that controlling dew point was the most important way of limiting the growth of microorganisms. The USEPA [24] recommends a relative humidity of 30-50% for residences.

In order for microorganisms to pose a respiratory health hazard, they must be dispersed into the indoor air. The use of HVAC systems in buildings and use of humidifiers and vaporizers in residences can promote the dispersion of bioaerosols growing in stagnant water reservoirs. In the conference room of an office building, the level of airborne fungi was 240 colony forming units (CFU) per m^3 when a small air handling unit was not in operation; when the unit was turned on, levels of fungi increased to 1,650 CFU/m^3 [26]. If reservoirs of microbiological contamination are disturbed, the amount of material released to the air increases dramatically. For example, in a poorly maintained cooling-coil section of an air-handling unit, slight agitation of the heat-exchanger surfaces increased the number of airborne fungal spores four orders of magnitude (from 2,000 spores/m^3 to 13,000,000 spores/m^3). [27] In another example, turning on a fan-coil unit and bumping its outside surface (analogous to backing a chair into the unit), increased the airborne fungal spores more than tenfold, from 7,300 CFU/m^3 to beyond the measuring capacity of the sampler (*i.e.*, >94,000 CFU/m^3) [27]. Spores may also accumulate on the interior surfaces of heating duct systems, and the use of forced-air heating systems can generate bioaerosols.

In addition, currents from forced-air systems (winter use) and circulating fans (summer use) may resuspend bioaerosols found in household dust, such as dust mites or animal products. The USEPA [24] and others [25] have emphasized the importance of keeping residences clean to reduce the amount of accumulated allergens. Elderly or infirm individuals may have reduced physical ability to maintain a clean household. Thus, increased air movement could also increase the level of airborne biological contaminants. As noted, the "personal cloud" effect can increase particle concentrations by as much as 100%.

Several studies have linked HVAC systems to outbreaks of hypersensitivity pneumonitis and other respiratory diseases [26-27]. Microbiological contamination has been found in HVAC ductwork, humidifiers, air washers, and fan-coil units. In an office building, mass illnesses (headaches, muscle

aches, fever, chills, nausea, wheezing, and chest tightness) of at least one-third of the employees were correlated with the activation of the HVAC system on three separate occasions [24]. The employees became ill within 24 hours of HVAC activation. Outbreaks of respiratory distress from bioaerosols are not confined to large building ventilation systems and can also be traced to microorganisms growing in home heating and cooling systems and humidification devices.

Household mold and dampness have been evaluated as a risk factor in respiratory health effects. Three large studies have been conducted in the U.S. [28,29] and in Canada [30]. In both studies, questionnaires were used to collect information on the extent of mold and dampness and on respiratory health among children [28; 30] and adults [29]. After adjustments for smoking habits, age, gender, residence, parental education, heating fuel (Canadian study only), and cooking fuel (Canadian study only), odds ratios for various respiratory conditions were determined. For U.S. children, [28] the odds ratios for molds ranged from 1.27 (asthma: 95% C.I.= 0.93, 1.74) to 2.12 (cough: 95% C.I.= 1.64, 2.73); for dampness, the values ranged from 1.42 (asthma: 95% C.I.= 1.04, 1.94) to 2.16 (cough: 95% C.I.= 1.64, 2.84). For Canadian children, [30] the odds ratios for molds/dampness ranged from 1.32 (bronchitis: 95% C.I.= 1.06, 1.39) to 1.89 (cough: 95% C.I.= 1.58, 2.26). For Canadian adults, [29] the odds ratios for molds/dampness ranged from 1.45 (chronic respiratory disease: 95% C.I.= 1.29, 1.64) to 1.62 (lower respiratory symptoms: 95% C.I.= 1.48, 1.78). Taken together, all three studies demonstrate an excess risk of respiratory distress associated with household dampness/molds. The relatively high odds ratios suggest that any exposure misclassification due to indoor-mold exposure could impact the interpretation of PM epidemiology studies. That is, the PM effect detected by the mortality/morbidity studies is so subtle that it would require only a small confounding effect from concomitant indoor-air exposure to produce the reported results.

The concentration and speciation of bioaerosols are affected by seasonal variations and weather conditions. For example, in Japan, 74% of those cases of hypersensitivity pneumonitis requiring hospitalization occurred during the summer in hot, humid climates. [25] In another example, air sampling of a large building in which one of the occupants was experiencing allergic respiratory disease, revealed differences between summer and winter. In the summer, the total CFU/m^3 was 1,400 and was dominated by *Sporobolomyces* spores, in the winter, fungal spore counts were only 20 CFU/m^3 and were dominated by unidentified yeasts. This building was located in a climate characterized by high summertime humidity and an HVAC system that was poorly maintained. In addition, the intensity of use of any climate-control system is linked to outdoor conditions. The WHO [23] also has stressed that climate and weather are critical when evaluating microorganism exposure.

BIOLOGICAL PLAUSIBILITY FOR VARIOUS PM

The ambient PM mix varies in chemical and size composition, both regionally and seasonally. Particulate-matter epidemiologic studies have been conducted in numerous locations in the US, each with a different PM mix. In each study, it was not possible to determine which component of air pollution was responsible for the observed effects in mortality and morbidity. There has been tendency to imply that the smaller (2.5 μm) combustion-derived particles are more toxic than the larger, crustal-derived particles. [5] For example, the reported lack of respiratory problems during dust storms (> 1,000 $\mu g/m^3$) in Eastern Washington State [31] has been noted as evidence that crustal particles and particles predominantly larger than 2.5 μm are less problematic than combustion-derived particles and the $PM_{2.5}$ fraction. Yet, this same evidence indicates that people can be exposed acutely to high levels of particles and not develop signs of illness. Moreover, the crystal-particle concentrations are not correlated to human behavior patterns to the extent that other sources are, a fact that supports the "alternative causation" interpretation of the epidemiologic associations.

It also has not been possible to identify the mechanism(s) by which "generic" PM might exert an effect. Because of the very low PM levels associated with health outcomes in the epidemiologic studies and because of the short latent period, it makes sense to consider allergenic, irritant, or infectious mechanisms of action. The dose of particles available at ambient PM levels is not sufficient to induce frank pathology. An individual breathing for 24 hours inhales a total air volume of about 20 m^3. If the PM concentration is 50 $\mu g/m^3$, and the deposition efficiency is approximately 25%, then the mass deposited in the lungs is 0.25 mg. Even if this amount is 100% bioavailable, the systemic daily dose would be only 0.0035 mg/kg for a 70 kg person. For systemic effects, this can be compared to chemical-specific "reference doses" (RfDs) which are toxicity factors for noncancer effects and represent the daily intake that EPA has determined can be maintained continuously without expectation of any adverse health effects. The scarcity of such potent substances is supported by an examination of EPA's Integrated Risk Information System (IRIS) data base, which reveals that only a small subset of the toxic chemical substances listed have RfDs less than 0.0035 mg/kg-day. Only a fraction of this subset of chemicals could plausibly act *via* the respiratory tract to produce the endpoints that are the subject of the PM epidemiology studies (*e.g.*, lethality). The RfD incorporates several safety factors and is manyfold (100× to 10,000×) below frank-effect levels; calculated systemic doses from continuous inhalation of 50 $\mu g/m^3$ PM do not result in doses approaching typical RfDs.

For pulmonary effects, the local dose to lung tissues can be estimated from the fact that 0.25 mg represents 4.8×10^8 unit-density, 1 μm diameter particles (each weighing 0.0005 ng), or 1.8×10^7 unit-density, 3 μm diameter particles (each weighing 0.014 ng). Although deposition in the lungs is not completely homogeneous over the surface area of the lung (140 m^2), the 50 $\mu g/m^3$ would yield an average dose of 0.0018 nanograms per mm^2, or 1 particle per day per 0.3 mm^2 lung surface for 1-μm diameter particles, or 1 particle per day per 8 mm^2 lung surface for the 3-μm diameter particles. These approximate calculations illustrate that there is little opportunity for extensive particle-to-lung-cell contact. Although these calculations assume uniform distribution of deposited particles, they also assume continuous exposure (*i.e.*, 24 hours) to outdoor air and do not take into account any removal processes (*i.e.*, dissolution, mucociliary transport, macrophage ingestion). With the exception of allergens, irritants, and infectious agents, the identity of such potent substances capable of eliciting the reported mortality/morbidity effects at such low doses over such a short time frame, remains elusive. This compromises the plausibility of ambient PM associations being causal.

Current toxicologic data and dose considerations do not implicate ambient PM as a plausible factor in the reported increase in daily morbidity/mortality. In contrast, toxicologic or epidemiologic data for ETS and bioaerosols are supportive of the potential for adverse health effects. It is also worth noting that from 1980 to 1987, asthma prevalence rates increased by 29% in the general population. For persons under 20 years of age, asthma rates increased 45%. [32] However, for a similar time period, 1985 to 1993, outdoor PM_{10} concentrations have decreased and in some regions (Southwest and Northwest) the concentrations have decreased by as much as 50%. [5] On the one hand, these data show that trends in asthma prevalence do not correlate with the trends in ambient PM levels. On the other hand, exposure to indoor, climate-controlled ("air-conditioned") air has gone up over this time period. Smoking prevalence among women also has increased during this time period, resulting in higher levels of ETS exposure in homes.

Environmental Tobacco Smoke

The contribution of ETS to respiratory disease has been stressed by the USEPA. [33] The agency has estimated that ETS exposure is responsible for 150,000 to 300,000 cases of respiratory tract infections in children less than 18 months of age. The agency also estimated that 200,000 to 1,000,000 asthmatic

children are affected by ETS exposure, and that ETS is a risk factor for new cases of asthma in children. These figures represent only rough estimates, and effects in children may not be directly relevant to the PM-mortality associations. The point worth noting, however, is that the failure to include ETS as part of PM exposure may distort the magnitude of respiratory effects attributed to ambient PM for those persons residing with smokers. Furthermore, if people (both smokers and non-smokers) spend more time indoors during episodes of air pollution and/or inclement weather, ETS exposures would be greater than under pleasant outdoor conditions.

Bioaerosols

Exposure to indoor biological contaminants has been linked to respiratory conditions, such as asthma and hypersensitivity pneumonitis. Furthermore, the same subpopulations (that is, the elderly and persons with lung diseases) that were identified as being at greater risk for ambient PM, were also noted by the USEPA [24] and WHO [23] as being particularly sensitive to biological aerosols.

The presence of skin-test reactivity to various bioaerosol allergens represents a measure of exposure to and development of an allergic-mediated sensitivity to the allergen. The prevalence of skin-test reactivity in school-aged children has been estimated as 30% for house-dust mites, 25% for animal danders, 20% for molds, and 5% for cockroach aeroallergens. [25] Thus, a significant proportion of children have acquired a sensitivity to these indoor-air, household antigens. Their reaction upon sufficient exposure could include allergic rhinitis, sinusitis, allergic dermatitis, or importantly, asthma; the presence of skin test reactivity is considered a strong risk factor for asthma.

The NAS report [25] on indoor allergens described additional evidence linking indoor-airborne antigens to antigen sensitization and asthma attacks. Clinical visits by allergic and atopic asthmatics correlated with the dust-mite growth curves in their homes. Among residents, *Alternaria* skin-test reactivity increased the risk 200-fold of sudden respiratory arrest in asthmatics during the *Alternaria* season for the region. The USEPA [24] has estimated that at least 200,000 emergency-room visits a year by patients with asthma can be attributed to exposure to house-dust mites, animal-related allergens (animal dander and cat saliva), and mold.

Prevalence rates for hypersensitivity pneumonitis are not known for the general population. [25] Prevalence rates in office workers, however, range from 1.2 to 4%, and one report indicated that 15% of the workers exhibited pulmonary disease from thermophilic *Actinomycetes* originating from a contaminated HVAC system. [25] Likewise, general prevalence rates for humidifier fever are not known. In the workplace, outbreaks are rare, but the attack rates are high (30 to 75% of the exposed workers). [25] The prevalence of hypersensitivity pneumonitis in homes has not been determined, but there are case reports of residents developing the disease. One nearly fatal case in an eleven-year girl was attributed to presence of thermophilic *Actinomycete* spores residing in an evaporative-type air cooler. [34] Such cooling units are widely used during the summer in the West, where temperatures are high and the humidity is low. In another case of, the presence of the disease coincided with the heating season, and thermophilic *Actinomycete* organisms were isolated from the furnace humidifier. [35] Removal of the furnace with its humidification system eliminated all indications of the respiratory disease.

Because of the allergenic nature of the mechanism of action of bioaerosols, the dose needed to elicit a response is very low, especially in the already-sensitized individual [20, 22]. In five office buildings reporting hypersensitivity pneumonitis-like illnesses or other respiratory distress, microorganisms could be identified either in the air or within components of the HVAC system; indoor levels of either respirable or total particulate were less than 50 $\mu g/m^3$ [24]. Thus, respiratory illness can

occur even when indoor-particulate levels are very low. In the case of cat allergens, airborne levels ranged from 2 to 20 ng/m^3 in houses with cats. During air disturbance, levels increased (40 ng/m^3) and the resulting dose was similar to that which can elicit a positive response from bronchial provocation tests. [36] In contrast to cat antigens, dust mite antigens were virtually undetectable in households where there was no air disturbance. [22] Upon disturbance, however, levels rose to 5 to 200 ng/m^3, depending on the nature of the disturbance. Thus, for both cat and dust mite allergens, airborne concentrations are a function of air movement.

SUMMARY AND CONCLUSIONS

Several recent epidemiology studies have reported small positive associations of mortality with ambient levels of PM. However, because of an inability to identify a specific toxic agent that can be validated by laboratory studies, it has not been possible to attribute causality to ambient PM. Lung tissue doses for ambient, low levels of PM are so small as to undermine the biological plausibility that ambient PM is responsible for the observed effects. Therefore, we propose that alternative pathways may link some other toxic agents with the observed effects and that the correlation with increased ambient PM levels is coincidental. The questions we posed are *"Why are there day-to-day fluctuations in PM?"*, and, *"Will not the same factors that cause such fluctuations in PM also signal changes in human behavior and exposure, which may be causally linked to morbidity and mortality?"* In particular, we have focused on indoor-air contaminants as potential offending agents.

Links among ambient PM levels, indoor-air quality, and adverse health effects remain unexplored. However, various relationships are conceivable. First, Americans spend the majority of their time indoors. Second, periods of elevated PM may correspond to inclement weather; both weather stress and/or outdoor air quality could further increase the amount of time spent indoors. Third, either heat or cold stress may lead to the increased use of climate-control systems. The use of such systems increases exposure to bioaerosols. Fourth, for those persons residing with smokers, increased time indoors results in more exposure to ETS. Fifth, and most importantly, both bioaerosols and ETS have been implicated in respiratory dysfunction. The epidemiology and toxicology of these two types of contaminants support biological plausibility. Studies have shown that people spend most of their time indoors and that biologically active are bioactive at ambient concentrations. However, the degree to which changes in human activity patterns and changes in exposure scenarios coincide with fluctuations in ambient PM remains to be established.

Because the magnitude of the reported increases in mortality/morbidity associated with ambient PM is so low, it would take minimal confounding by alternative exposure scenarios to produce the reported results. For example, if only 3 out of 100 deaths occurred during a 24-hour increase of 50 μm/m^3 PM during a winter cold spell, it is conceivable that those three persons could have turned on a humidifier for household winter dryness, started up a non-vented kerosene stove for heat, or decided to vacuum because they were "stuck" indoors. All of these activities generate indoor PM, some of which are biologically active at low concentrations.

If ambient PM is just a marker for weather changes and changes in human activity patterns, it would clarify three puzzling aspects of the current PM controversy:

- Lack of threshold: Given the low levels of ambient PM, it makes little toxicological sense that no threshold is observed. Yet, if the causality derives from a causative factor prior to increases in ambient PM, then the observed absence of a threshold with PM concentration itself would be reasonable.

- Similarity of associations across different cities, climates, countries: How could the "toxin" in PM be reproduced in such a wide variety of settings? Again, if the causality derives not from the PM itself, but from human factors and weather factors that "drive" PM fluctuations, the universality of the associations becomes more clearly understood.

- Lack of toxicologic mechanism: Humans occupationally exposed to particulate levels 100× greater than ambient PM do not experience instant death. Also, results from animal studies do not elucidate a mechanism by which small daily fluctuations of ambient PM can cause mortality and morbidity. If ambient PM is only a marker for other factors, then this dilemma is explained.

Human activity patterns and the strength of anthropogenic particulate emission sources are necessarily correlated. [37] Also, weather fluctuations correlate to both outdoor PM levels and the airborne levels of indoor PM toxins. Thus, it is highly plausible that the reported correlations of morbidity and mortality with daily PM concentrations are merely a reflection of other causal relationships that underlie both daily PM changes and daily fluctuations in morbidity and mortality.

The misidentification of the causal factor in the PM *versus* morbidity/mortality associations can result in costly mis-allocation of public health resources if ambient PM is targeted for stringent control. A recent analysis of the cost-effectiveness of life-saving interventions in the United States compared the cost per year of life saved of 587 interventions, guidelines, and regulations. [38] These interventions ranged over medical preventive measures, injury reduction, toxin control, and consumer protection. The median cost-effectiveness of proposed and implemented government regulations varied widely by government agency. In comparison to primary prevention expenditures in health care, medians by agency were as follows:

Health care, primary prevention	$5,000	per life-year
Federal Aviation Administration	$23,000	per life-year
Consumer Product Safety Commission	$68,000	per life-year
National Highway Traffic Safety Administration	$78,000	per life-year
Occupational Safety and Health Administration	$88,000	per life-year
Environmental Protection Agency	$7,600,000	per life-year

Given the fact that, by this analysis, the EPA already mandates expenditures per year of life saved that are 10 to 20 fold higher than any other agency, it would be unfortunate to add yet additional levels of expenditure and societal costs unless the public health benefit is clearly established. These figures illustrate the importance of examining very carefully the causal basis of the PM associations driving the recent impetus toward regulatory change in the National Ambient Air Quality Standards (NAAQS).

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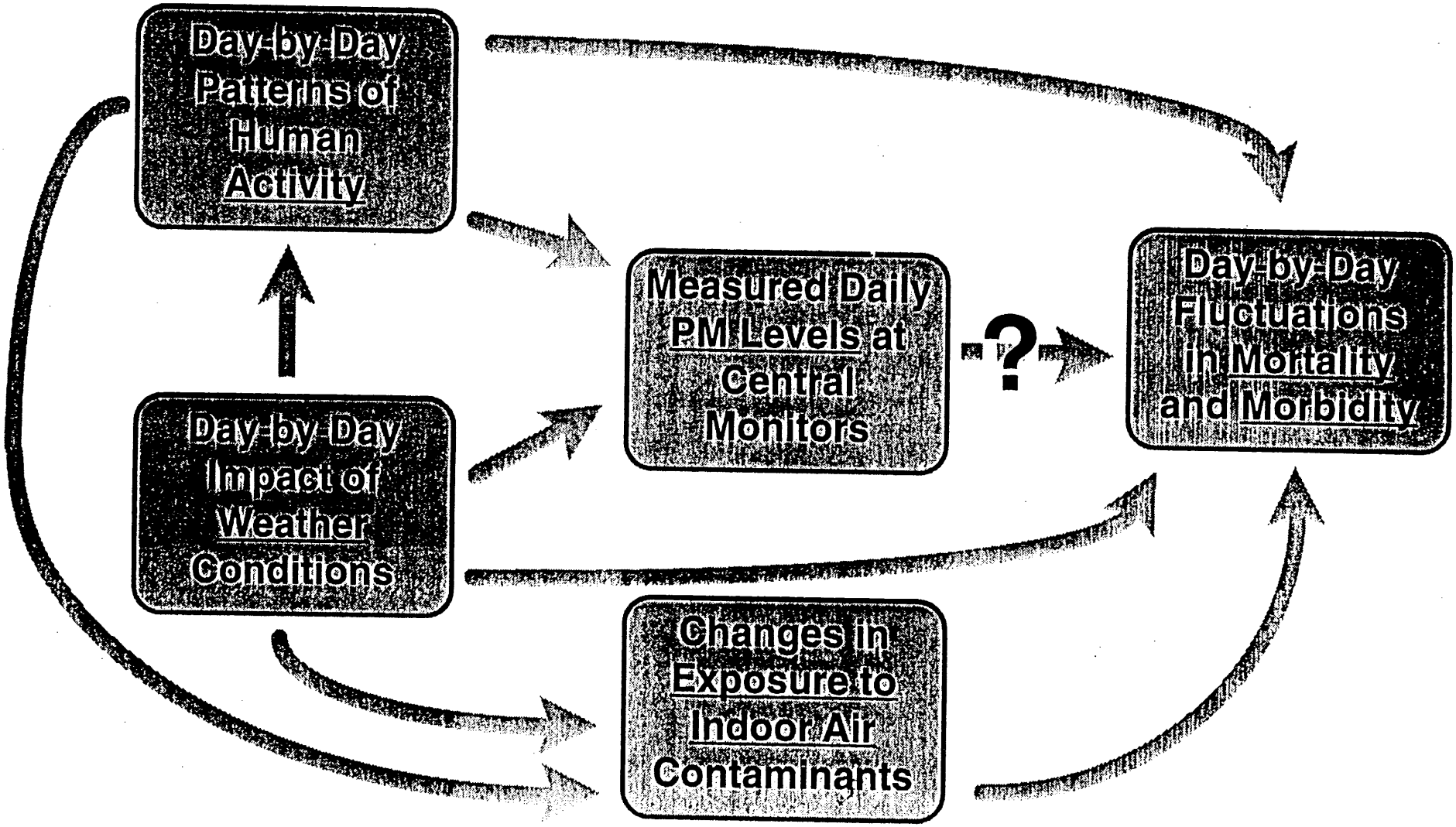

Figure 1
Several Pathways Can Cause Fluctuations in Daily Mortality and Morbidity

Relationships among EPA sampling methodologies for PM_{10} and $PM_{2.5}$; and their associations with meteorological variables (temperature, wind-speed, relative humidity)

Dagan Wright, Dean Lillquist, Jeff Lee, Ken Boucher

Rocky Mountain Center for Occupational and Environmental Health, University of Utah

Introduction

Health effects form particulate matter have suffered from lack of data on individual exposure. Furthermore limitations in source modeling exist. Source modeling is based on three components: emissions models, meteorological models, and air quality models .[1] Source modeling deficits include spatial variation in environmental measurements, incomplete information on chemical composition, and inadequate computer modeling.[1] Source modeling is dependent on the validity of EPA approved sampling methods.

Even with the strict EPA guidelines for environmental sampling of PM_{10} and $PM_{2.5}$, variations between sampling methods exist. The purposes of this study are to observe variations occurring in measurements between the EPA sampling methods (especially between manual verses automated methods) and to account for some of the variations using meteorological variables.

There are various sampling strategies for particulate matter. The following EPA reference and equivalent methods were used in this study:

- Manual and EPA reference sampler: Sierra-Anderson or General Metal Works Model 1200 PM_{10} High-Volume Air Sampler System (HIVOL)
- Manual and EPA reference sampler: General Metal Works G241M PM_{10} Dichotomous Sampler (DICOT)
- Automated and EPA reference sampler: TEOM Series 1400 PM_{10} (TEOM)
- Automated Sampler and equivalent sampler: Anderson Instruments Model FH621-N PM_{10} Beta Attenuation Monitor (BETA)

The EPA has developed a standard protocol for approving or disapproving a particular methods for sampling. The EPA compares the other methods to the reference method (HIVOL) in various sampling

conditions. The HIVOL is also used by the state as the "gold" standard. The sampling conditions, being conducted, range from inside a wind tunnel to actually being field tested.[2] The EPA uses regression analysis to determine the correlation between reference and equivalent methods.[3] If the method meets the EPA criteria (± 10 percent of the reference readings), it is designated as an equivalent method and is eligible to become a reference method. The reference methods (HIVOL and DICOT) require manual handling of the filter and specified period of time in a conditioning chamber. Both the TEOM and BETA are automated equivalent methods, although TEOM has been designated a automated reference method .[4] Potential for variations in measurements exist between the manual and automated methods since they measure particulate matter in very different ways. While the HIVOL and DICOT use similar sampling strategies, it is important to be aware of the possible sources of sampling error by understanding how the TEOM and BETA measure particulate matter.

The TEOM (tapered element oscillating microbalance) uses quartz crystal microbalances to directly measure particulate mass. A filter cartridge located on the end of a tapered tube collects the particulate. The wider end of the tapered tube is fixed, and the filter is located on top of the opposite end. The top of the tube continually oscillates. Air is passed at a given temperature (either 50 or 30 degrees centigrade) through a quartz filter on which particulate matter collects. The high temperatures are maintained to stay above the dew point and drive off humidity of the incoming air. As the mass of the filter end changes, the frequency changes. The mass is determined directly and inertially from the change in oscillation .[5] The relationship between frequency and mass uptake is not linear, but is known. The TEOM instrument is shock mounted to minimize effects from external vibration .[5] The precision of co-located TEOM samplers has been demonstrated in side by side sampling with standard deviation of plus or minus 0.5 $\mu g/m^3$.[5] When compared to the Wedding high volume and Sierra-Anderson dichotomous sampler in past studies, the TEOM readings were highly correlated to both of the samplers.[5]

The BETA takes air in through the inlet to the continuous tape reel of fibrous glass or Teflon membrane. The air must be heated to 303K (30 degrees centigrade) to prevent errors due to temperature or humidity.[6] The flow rate is maintained at 16.7 liters per minute. A ^{14}C source is used due to its long half-life and consistent emissions. Before sampling begins, the sampler determines the penetration of β particles through the sampling medium. At the end of sampling, the β-particle penetration is observed. From the difference between initial and final readings, the mass can be determined. The BETA collects particulate mass on filters. The calibration of mass is sensitive to other characteristics than mass .[5] Characteristics include air density (controlled for by setting the thermoregulation at 303 K on the inlet), the presence of radioactivity from the collected particles, and variability of the mass absorption coefficient.[6]

Other events can be associated with variations in the measurements between the methods, even if strict sampling/handling methods are followed. Despite the above information, many concerns have been arisen in using heated air and different filter types for measuring particulate matter. Brooks, L.R, et al. (1992), demonstrated the different filter types effects on recovery of particulate matter.[7] There were variations in recovery of organics/mutagens on different filter types.[7] The Teflon impregnated glass fiber filters recovered more organics/mutagens than the quartz counterparts .[7] This one variation may offset results from reference and equivalent methods.

Meyer, Michael B., et. al. (1992) discovered, in an area with significant amounts of wood smoke, a systematic difference between the HIVOL and the TEOM measurements.[8] The study found evidence to support that partial volatilization of organic compounds can account for much of the variability between the HIVOL and TEOM methods[8]. This phenomena may have more effects on fine particulate matter ($PM_{2.5}$), because fine matter mostly consists of particle bound organics .[9] The use of fine particulates ($PM_{2.5}$) is currently being reviewed by the EPA for future use in air quality standards. Patashnick,

Harvey, et. al. (1990) attributed the difference of results, when comparing TEOM to HIVOL measurements, to a lower presence of high vapor pressure organics/volatiles .[9] Meyer, Michael, et. al. (1995) used two temperature settings and two flow rate settings (50 and 30 degrees centigrade, 3 and 1 liter per minute). The lower sampling temperature/flow rate (30 degrees centigrade and 1 liter per minute) had a higher correlation to the reference standard (HIVOL) .[10] The different results in exposing the filter to a non-constant reference temperature between sampling methods needs more research .[10] The California EPA found measurements in a dry lake bed showed a poor correlation between the TEOM and HIVOL.[11] In reviewing this study, the correlation was based only on three days of 24 hour averages, with a total daily sample size of three.

Some attempts have been made to account for some of the variation using meteorological variables. In past TEOM sampling for this site and other sites in the state, the raw TEOM data has been corrected due to speculation that the meteorological temperature of the outside air affects the raw TEOM measurements. Correctional factors using average monthly temperature have been used only for the TEOM sampler. The use of a correction factor creates an adjusted TEOM value which is used to predict the 24 average of HIVOL values on days with a high PM_{10} level. By predicting what the HIVOL may read early in the mornings, proper strategies can be implemented to keep the particulate levels below EPA standards.

The following hypotheses are addressed in the study. First the variability, of TEOM readings compared to HIVOL readings, has linear associations with various meteorological variables such as relative humidity, temperature, and wind speed. Second, the adjustment factor the state uses for TEOM readings over predicts the measurements recorded by HIVOL. Third, the variability of the ratio of $PM_{2.5}$ to total DICOT (PM_{10}) is linearly associated with the meteorological factors of relative humidity, temperature, and wind speed.. Fourth, the relationship of $PM_{2.5}$ to total DICOT (PM_{10}) is linearly associated with the relationship of HIVOL to TEOM measurements. Finally a correlational analysis between the automated methods will determine which sampler came in closer agreement to the HIVOL.

Methods

All the data was collected from Lindon, a sampling site in Provo, Utah. [12, 13] Both state instrumentation location and private instrumentation location were at this site within meters of each other and set up according to EPA specifications. The stations are located within a residential area near a school. The stations included the four particulate matter sampling instruments and the meteorological instruments.

The samples for the four particulate sampling instruments and the meteorological instruments were taken from January 1, 1994 to March 31, 1995. Daily samples were recorded from January 1, 1994 to March 1, 1994 and from November 1, 1994 to March 31, 1995. During the remaining time periods, measurements were taken every third day except for September and October of 1994 when the station closed for routine maintenance. Any missing data occurred on a random basis. Data, corresponding to the sampling period of the DICOT sampler, was only included, because of this paper's focus on including measurements of PM_{10} and $PM_{2.5}$.

Meteorological data, including temperature in degrees centigrade, relative humidity, and wind speed were recorded by the state Met One Instruments System. Each measuring instrument produces a signal to the Model 2270 Multi-Met Translator Module. The Model 2270 Multi-Met Translator Module provides power to the various sensors on the station as well as conditions the sensor data to be used by the recorder/data logger. The following instruments were used to measure the environmental variables of temperature, relative humidity, and wind speed: Model 083-0 Relative Humidity Sensor, Model 060A-2 Temperature Sensor, and Model 010B Wind Speed Sensor. The Temperature and Relative Humidity sensors are anchored within the Model 076B, a Motor Aspirated Radiation Shield. A routine maintenance/calibration check was performed, according to manufacturer and EPA guidelines on the meteorological equipment in September and October of 1994 along with the change over to the Beta Gauge.

The Sierra-Andersen or General Metal Works Model PM_{10} High Volume Air Sampler System (HIVOL) was used by the state for the reference method. Sampling time occurred from twelve midnight to twelve midnight. The flow rate was 1.13 m^3/minute. The type of filter was a quartz fiber made by Whatman. The dimensions of the filter are eight inches by ten inches. At the end of the sampling period the filters were folded in half and placed in an unsealed envelope. Every couple of days, the filters were picked up and brought to the Department of Air Quality located in Salt Lake City. Each filter was conditioned according to the standard EPA protocol before weighing. This HIVOL was used for the entire period of this study. The HIVOL was routinely calibrated and maintained according to EPA and manufacturing guidelines.

The DICOT data was located only meters from the state station. The sampler was a General Metal Works G241M PM_{10} Dichotomous Sampler (DICOT). Sampling time was from twelve midnight to twelve midnight. The flow rate was approximately 1.46 m^3/minute. The particulate matter was collected on eight inch by ten inch QMA quartz fiber filters made by Whatman. After the sample was collected, the filter was folded in half and stored in its original container (a glassine cover inside a manila envelope). The envelopes were then sealed in a Ziplock freezer bag to be stored at a temperature of <-5°C until they arrived at the lab for weighing. After a batch of 25 samples had been collected, the filters would be sent off to the lab. The samples were taken on a daily basis starting from January 11, 1994 to March 1, 1994 and from November 1, 1994, to March 10, 1995. During the interim time, samples taken every third day. This DICOT was used for the entire period of this study. The DICOT was routinely calibrated and maintained according to EPA and manufacturing guidelines.

The TEOM Series 1400 PM_{10} Monitor is used by the state. The flow rate was 16.7 liters per minute with 3 liters per minute reaching the filter. The filter used was a cassette quartz fiber filter provided by the

company. The remaining flow was bypassed. The heated air inlet was set at 50 degrees centigrade. The sampling time was from twelve midnight to twelve midnight the next day. Readings were taken on an hourly basis. The 24-hour average was obtained by taking a total of the hourly readings and dividing by 24. In this study the TEOM monitor was used from January 1, 1994 to October 1994. The TEOM was routinely calibrated and maintained according to EPA and manufacturing guidelines.

Data for the TEOM consists of two entries: raw data and adjusted data. The raw data is what the instrument reads. The adjusted data is the result of an adjustment factor used by the state of Utah, which is different for each month. The purpose of the adjustment factor was to create a value closer in agreement with the results of the HIVOL

The correction factor was obtained by taking the average monthly temperature and applying it to the following equation: $Y = [X \times (-3.52) + 87.25 / 100] + 1$ X = Avg. monthly temperature Y = Correction Factor . The correlation coefficient of the above equation is 0.58, and based on 130 data points. Table I lists the average monthly temperatures and correction factors.

Table I Correction Factor Table

Month	Average Temperature (deg C)	State TEOM Correction Factor
January	-1.9	1.94
February	1.2	1.83
March	4.8	1.70
April	9.6	1.53
May	14.9	1.35
June	20.2	1.16
July	25.3	0.98
August	23.8	1.03
September	18.3	1.23
October	11.7	1.46
November	4.3	1.72
December	-0.9	1.90

Since November 1, 1994, the Anderson Instruments Model FH621-N PM_{10} Beta Attenuation Monitor (BETA) has been used at the site. The flow rate was 16.7 liters per minute over the filter. The air inlet is heated to 303 Kelvin or 30 degrees centigrade. The filter consisted of a Teflon-coated glass substrate. Measurements were recorded on an hourly basis. A 24 average was calculated and reported. The BETA was routinely calibrated and maintained according to EPA and manufacturing guidelines.

Descriptive statistics were run on all the variables including: HIVOL, total DICOT, $PM_{2.5}$ / total DICOT (PM_{10}), BETA, raw TEOM data, adjusted TEOM data, the ratio of raw TEOM to HIVOL data, and the ratio of HIVOL - raw TEOM / raw TEOM. In addition an average monthly temperature was also determined for other uses in the study. The descriptive statistics give a different perspective of the site characteristics and will be used for other parts of the study, including evaluation of automated sampling methods.

A correlational analysis, using the bivariate Peerson technique, observed the relationships of HIVOL measurements, DICOT measurements, raw TEOM measurements, adjusted TEOM measurements, and BETA measurements. This was done to compare automatic sampling techniques (reference and equivalent methods) to the manual sampling techniques of DICOT and HIVOL (reference methods). In addition, a one paired-samples t-test was performed on the differences between an adjusted TEOM value and the HIVOL value to show there is a significant difference in average values.

Multiple regression analyses in this study used the meteorological effects of temperature, humidity, and wind speed as independent variables. The dependent variables used were: the difference of a HIVOL and raw TEOM divided by the raw TEOM value, the ratio of HIVOL to raw TEOM values, and the ratio of $PM_{2.5}$ to total DICOT. The resulting information was then used to create a model to account for some of

the variations in the independent variables. Linear regression analyses was run on individual independent variables.

The comparison of the TEOM monitor to the HIVOL was used in observing the relationships to meteorological variations for the following reasons: the heated air inlet temperature was higher (50° C) than the BETA gauge (30° C) heated air inlet and the use of an adjustment factor for TEOM was of interest.

Results

The linear regression analyses, using one model that took all three meteorological variables (temperature, relative humidity, and wind speed) into account and another model taking only temperature into account, for the variability of raw TEOM values to HIVOL yielded statistically significant results ($p < 0.05$). The model, including all three variables, was associated ($r^2 = 0.27$) with the variability between the TEOM and HIVOL readings. If only temperature was taken into account, the other model also had a slightly lower association ($r^2 = 0.19$). See Table II and Table III for more statistical information. The equations were created from models:

HIVOL = (0.210 + 0.020*temperature + 0.003*relative humidity + -0.49*wind speed +1.00) * raw TEOM

HIVOL = (0.243 + 0.014*temperature + 1.00) * TEOM

Table IV shows the correction factor created by the model's equation obtained from Table III, using the same average monthly temperatures as the state.

Table II Multiple Meteorological Model

Dependent variable: (HIVOL - raw TEOM) / raw TEOM

Independent variables: Temperature, Relative Humidity, and Wind Speed

R-square	0.26869
Constant Parameter Estimate	0.210239
Temperature Parameter Estimate	0.019719
Temperature Prob > [T}	0.0001
Relative Humidity Parameter Estimate	0.003198
Relative Humidity Prob > [T}	0.2082
Wind Speed Parameter Estimate	-0.048710
Wind Speed Prob > [T}	0.0025
Sample size	90

Table III Temperature Meteorological Model

Dependent variable: (HIVOL - raw TEOM) / raw TEOM

Independent variable: Temperature

R-square	0.18830
Constant Parameter Estimate	0.242909
Constant Standard Error	0.041452
Temperature Parameter Estimate	0. 014044
Temperature Prob > [T}	0.0000
Sample size	92

Table IV Study correction factors

	Average Temperature (deg C)	State TEOM Correction Factor	Study TEOM Correction Factor
January	-1.9	1.94	1.22
February	1.2	1.83	1.26
March	4.8	1.70	1.31
April	9.6	1.53	1.38
May	14.9	1.35	1.45
June	20.2	1.16	1.52
July	25.3	0.98	1.60
August	23.8	1.03	1.58
September	18.3	1.23	1.50
October	11.7	1.46	1.41
November	4.3	1.72	1.30
December	-0.9	1.90	1.23

Using descriptives and the paired t-test, the TEOM adjusted values and HIVOL values were shown to be statistically different ($p = 0.0001$) and the average adjusted TEOM was 10 micrograms/m^3 higher than the corresponding HIVOL value. In addition, Table V shows that the average ratio of adjusted TEOM to HIVOL values was approximately 1.4; therefore on the average the state was over-predicting what the HIVOL would read by 1.4 times its actual reading.

Table V Sampler Descriptive Statistics

Variable	Mean	Standard Deviation	Range
adjusted TEOM/HIVOL	1.41	0.45	1.39
raw TOEM/HIVOL	0.76	0.25	1.83
HIVOL - raw TEOM / raw TEOM	0.37	0.26	1.92
BETA/HIVOL	1.01	0.03	2.38
HIVOL/DICOT	1.06	0.27	2.01

The ratio of $PM_{2.5}$ to total DICOT is only weakly associated ($r^2 = 0.09$), although statistically significant ($p = 0.0002$), with changes in a model including all three meteorological variables (temperature, relative humidity, and wind speed). In a model only using relative humidity as an independent variable, a weak, although statistically significant ($p < 0.0000$), association ($r^2 = 0.073$) was observed.

The association of $PM_{2.5}$ to total DICOT and raw TEOM/HIVOL was not statistically significant ($p = 0.098$) and an minimal association ($r^2 = 0.03$) was found.

In the correlational analysis comparing automated sampling methods to the HIVOL method, the BETA had a statically higher correlation to HIVOL among the two automated methods used. See Table VI for details.

Table VI Correlational Analysis among Samplers

	Correlation with HIVOL
DICOT	0.8929
BETA	0.9439
raw TEOM	0.9236
adjusted TEOM	0.7902

Finally the descriptive of $PM_{2.5}$ to total DICOT measurements shows wide variations exist between the two particle-size classifications at this site. See Table VII for details.

Table VII total DICOT/$PM_{2.5}$

	Mean	Number of observations	Standard Deviation	Range	Lowest	Highest
total DICOT/$PM_{2.5}$	0.507	235	0.186	0.721	0.174	0.895

Discussion:

The relationships observed variations in sampling methodologies and the possible effects of meteorological conditions. By understanding some of these relationships, a better sampling methodology can be set up to detect the particulate matter levels in the atmosphere that best represents exposure to the human population. One important issue addressed in the introduction is the standardization of sampling methodology among various techniques. One such example is to maintain a constant temperature that a filter is exposed to during sampling for the manual as well as automated methods. As stated in the introduction, a manufacturer of one of the automated sampling instruments is pursuing the issue of internal temperature exposure to the filter in all sampling methods.

Despite the EPA guidelines on proper sampling methodologies, there is room for error. In this study, the TEOM filter was exposed to a temperature of 50° centigrade while the BETA filter was only exposed to 30° centigrade. The difference in temperature could account from some of the variation in addition to the use of different sampling methodologies. The differences in the handling of the filter after sampling is complete is another possible source of variation. The state HIVOL samples were stored in an unsealed envelope at room temperature for a couple of days, while the DICOT samples were sealed and stored at less than -5° centigrade for a period of time before being shipped off for weighing. Another source of error could be the type of filter used. Since there are more than one filter type available, different filters may yield different results as discussed in the introduction. The quartz fiber filter, used by all samplers except the BETA would collect less organics/mutagens than the Teflon counterparts used by the BETA.

There was also room for error in using the correlation analyses, the t-test, and the multiple regression analyses. The assumption of a normal distribution is assumed. The associations could vary because the

all variables for each method are not normally distributed due to the levels recorded do not follow a normal distribution. A way to normalize the distribution would be to take increased numbers of samples over a greater period of time. In theory the larger sample size would create a closer approximation to a normal distribution. Using only a linear association in the multiple regression analyses could miss relationships that are not linear.

The variability, of the relationship of TEOM readings compared to HIVOL readings, does have a linear association ($r^2 = 0.27$) with a meteorological model that includes temperature, relative humidity, and wind speed. In addition all three variables did show an association with the variation, but temperature showed the greatest magnitude of association ($r^2 = 0.1$. The state factor, using only temperature for adjustment, is a good lead and has already created new ideas for research. An example in Table IV did show the difference of correction factors using the states average monthly temperature.

- Model for all three variables:

HIVOL = (0.210 + 0.020*temperature + 0.003*relative humidity + -0.49*wind speed +1.00) * raw TEOM

- Model for only temperature:

HIVOL = (0.243 + 0.014*temperature + 1.00) * raw TEOM

- State model that used average monthly temperature

HIVOL = raw TEOM * correction factor

These models can account for some of the variations between the TEOM and HIVOL method and lead to further insights into PM measurement.

In addition Table VIII describes the trends of association with the meteorological variables and the variations of TEOM to HIVOL. The different associations with relative humidity indicates the two variables may not act independently in this study.

Table VIII Sampler Variations and Meteorological Associations

	As temperature increased	**As relative humidity increases**	**As wind speed increased**
Model that included all three variables	The variation increased	The variation increased	The variation decreased
Model that used only one variable in each regression analysis	The variation increased	The variation decreased	The variation decreased

A paired t-test provided further insight into the state adjustment factor by showing the adjustment factor was over-predicting what the HIVOL would read by approximately 10 micrograms/m^3. Using descriptive statistics, the ratio of adjusted TEOM to HIVOL showed the state over-estimated the HIVOL by 1.409 times. The correlational analysis among the sampling methods found a higher correlation with the raw TEOM readings compared to the adjusted TEOM readings. Therefore the new models may provide a foundation to create a closer approximation to what the TEOM may read when they are used together.

Even though relative humidity and temperature are statistically significant in relation to the ratio of $PM_{2.5}$ to total DICOT, they have account for little variation (r^2 of 0.09). One interesting observation was noted in Chart 1. The scatter plot displayed an interesting pattern that the linear model could not mathematically model.

In theory and other studies, fine particles containing more volatile matter may show greater variation in recorded measurements between the TEOM and HIVOL samples. This is based on other research suggesting the heated air inlet on the TEOM may drive off some of the volatiles before reaching the filter to be measured.[10,11] This study found no linear association with $PM_{2.5}$ and variation between raw TEOM and HIVOL measurements.

There are many advantages to using an automated sampler. The automated method, recording on an hourly basis, allows the state to make more informed decisions to maintain acceptable PM_{10} levels before they get too high. It eliminates the risk of human error by requiring no handling of the filters before measurement. Instead of measuring only 24 hour averages, the regular interval recording of PM_{10} levels could provide additional insight into particulate matter behaviors and characteristics. Overall the BETA showed a higher correlation than the TEOM method (a EPA reference method) to the HIVOL at this site.

Another concern is the EPA is looking at $PM_{2.5}$ as a new standard. In the results section there appeared to be substantial variation in the ratio of $PM_{2.5}$ to PM_{10}. According to the data, it is not reasonable to estimate $PM_{2.5}$ to PM_{10} simply by recording the PM_{10} levels based on the descriptive statistics. The mean ratio showed approximately one half the mass of PM_{10} is composed of $PM_{2.5}$. It would be interesting to further investigate variations in the ratio on a monthly basis, at different PM_{10} levels, or in different seasons of the year. This might add further insight for the EPA to make a more informed decision on the standard. This type of relationship may provide further health information by allowing use of PM_{10} studies and estimating the approximate amount of $PM_{2.5}$ present.

This is an extensive data set that gives various perspectives on particulate matter behavior patterns as well as the relationships between different sampling methods. This above study can pave the road for further research in the field of particulate matter sampling methodologies, assessment of exposures, and particulate matter behavior.

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V. SESSION CHAIRS' AND OTHER COMMENTARIES

A. Investigational Methods; Epidemiological Findings
B. Toxicology; Deposition and Clearance; Mechanisms of Injury
C. Exposure Assessment and Sampling; Total Exposure
D. Other Commentaries

A. Investigational Methods; Epidemiological Findings

Investigational Methods

Robert F. Phalen
University of California, Community and Environmental Medicine,
Irvine, CA, 92697-1825, U.S.A.

Five platform papers were presented in the opening session. Although there was a focus on methods currently in use for evaluating the health effects of particulate air pollution, some papers also dealt with recent results from epidemiological investigations. The presentations were each followed by questions from the audience, and a general open discussion completed the session.

Paper 1.1: "Epidemiology Investigations of the Health Effects of Particulate Air Pollution: Strengths and Limitations"

The first paper, presented by C. Arden Pope, III (of Brigham Young University), dealt with the strengths and limitations of current approaches used in epidemiological investigations of particulate air pollution. It was stressed that the strongest evidence to date of the potential human health effects of particulate air pollution is the coherent pattern of the associations of cardiopulmonary effects with particulate air pollution monitoring data, as seen by several investigators in numerous cities. However, these studies have at least four inherent limitations including: 1) limited information about biological mechanisms, 2) relatively meager information regarding linkages between ambient and personal exposures, 3) difficulty of disentangling independent effects or potential interactions between highly correlated risk factors, and 4) inability to fully explore the relative health impacts of individual constituents of particulate pollution. Associations of cardiopulmonary health outcomes with particulate air pollution that have been observed in the epidemiological studies therefore provide only one important part of the full picture. A more complete understanding of the health effects of particulate air pollution will require additional key contributions from toxicology, exposure assessment, and other disciplines. Both the strengths and limitations of the epidemiological studies stem largely from the use of people who are living in uncontrolled environments, and who are exposed to complex mixtures of particulate air pollution.

Paper 1.2: "Toxicology Investigations: Strengths and Limitations"

The second paper, prepared by Joe L. Mauderly (of the Inhalation Toxicology Research Institute), was delivered by Richard Schlesinger (of New York University). The paper described the strengths and limitations of modern in toxicology studies. It was pointed out that the strengths and limitations of laboratory-based toxicology investigations of the health impacts of particulate air pollution are actually those common to all laboratory experiments. The greatest strength is the ability to dissect a complex problem into its component parts and conduct a sequence of

hypothesis-driven experiments which, together, yield an understanding of the processes by which phenomena observed in population studies occur. The accompanying weaknesses are 1) the difficulty of developing the correct hypothesis, and 2) the difficulty of constructing an experiment to address the hypothesis definitively. The second greatest strength is the ability to conduct the experiment under carefully-planned, well-controlled circumstances. The corresponding weaknesses are 1) the need to understand which variables to control, and 2) the danger of eliminating outcomes which require the interactions of variables which were eliminated. The third greatest strength is the ability to select the experimental model and the level of biological organization to study (eg, molecule, cell, tissue, organ, or the whole subject). The inherent weakness corresponding to this strength is the uncertainty about applicability of results from the model system to the real population or actual exposure situation of concern. Finally, the three cardinal responsibilities of the experimentalist are: 1) rationality with respect to the experimental design; 2) reliability of the results; and 3) the validity with which the results may be extrapolated to the population and exposure of concern. Unfortunately, there is often a tendency to dwell on the second responsibility and give insufficient attention to the first and third. It was concluded that toxicology and epidemiology are both empowered when conducted as a partnership.

Paper 1.3: "Are Combustion Particles Responsible for the Associations with Daily Deaths?"

The third paper, delivered by Douglas Dockery (of Harvard University), related to a question: "Are combustion particles responsible for the epidemiological associations with daily human deaths?" It was pointed out that although a score of studies have reported associations between airborne particles and daily deaths, they have not identified the specific characteristics of particles that may be responsible for these effects. Accordingly, a study was performed which investigated this question using fine and coarse particle mass concentrations measured every other day (for eight years) in each of six metropolitan areas (Boston, MA: St. Louis, MO; Knoxville, TN; Steubenville, OH; and Madison, WI). Hydrogen ion concentrations were measured daily for one year in each location. Poison regressions controlling for smooth functions of time, temperature, humidity, and indicators of day of week, rain and snow were estimated in each location, and the estimated pollution effects combined across cities. An interquartile range (IQR) change in PM2.5 (13.7 $\mu g/m^3$) was associated with a 2% increase in daily deaths (95% CI 1.5% to 2.7%). An IQR increase in sulfate particle mass (5.8 $\mu g/m^3$) was associated with a 1.2% increase (95% CI 0.7%-1.8%). In contrast, coarse mass (10.6 $\mu g/m^3$) defined as PM10 - PM2.5 and hydrogen ion (18.9 $nmole/m^3$) showed weak associations 0.5% (95% CI 0.1% to 1.1%) and 0.2% (95% CI 0.6% to 0.9%) respectively. These findings were interpreted as indicating that daily mortality is specifically associated with fine combustion particles, that these associations are not restricted to sulfate particles, and that the associations are not attributable to the total acidity of the fine particles.

Paper 1.4: Air Pollution and Mortality: Searching for a Threshold in the Association"

The fourth paper, presented by Luis Cifuentes (Catholic University of Chile) and coauthored by Lester B. Lave (of Carnegie Mellon University), dealt with the possible existence of a threshold level for effects of particulate air pollution. The paper acknowledged that a growing number of time-series analysis have shown an association between ambient concentrations of particulate matter and increased human mortality. Some of these studies have been used by the U.S. EPA as the basis of the proposed NAAQS standard for particulate matter. However, few of the studies have considered in depth the possible existence of a threshold (pollutant concentrations) in the effects. This work analyzed data for three cities that have different characteristics of weather and pollution: Philadelphia, PA; Birmingham, AL; and Santiago, Chile. Weather and seasonal effects were controlled for each individual cities, and also a single model was used across all cities. Particulate matter was measured as TSP (total suspended particulate mass) in Philadelphia, PM10 in Birmingham, and both PM10 and TSP in Santiago. Other pollutants included in the analysis were SO_2 and O_3 for Philadelphia, and SO_2, O_3 and CO for Santiago. The existence and level of a threshold was explored using three different approaches: (a) including a discrete variable representing the quintiles of particulate matter concentrations, (b) dividing the data in different subsets according to their particulate matter concentrations, and (c) modeling particulate matter concentrations as a continuous piecewise linear function. The results indicate an important influence of the observations with higher levels of particulate matter, and support the hypothesis of the existence of a threshold level in the associations.

Paper 1.5: "Particle Epidemiology Evaluation Project"

The last paper, by Jonathan Samet (of Johns Hopkins University), provided an update on the Particle Epidemiology Evaluation Project, which was begun in 1994 under the sponsorship of the Health Effects Institute (Cambridge, MA). The project was established to address critical issues related to the observational studies on particulate air pollution and mortality. It has two phases: Phase 1A which was directed at replication and validation of selected studies and Phase 1B which included analyses of the data for Philadelphia. Phase 1A was directed at replicating and validating selected published reports on particulate air pollution and mortality. The project included verifying one of the previously analyzed data bases (Philadelphia, 1973-1980), replicating analyses for key locales, and assessing the sensitivity of findings to analytic assumptions and model specification choices. The data set and analyses were replicated. It was also found that the qualitative effects of TSP and SO_2 were not sensitive to model specification; interdependence of their effects was not found.

In Phase 1B, it was shown that findings are relatively insensitive to the approach for control of effects of weather on mortality. The general findings with regard to pollution were unchanged, comparing empiric approaches with synoptic categorization of weather. In Phase 1B, a data set was also analyzed for Philadelphia, 1974-1988, which includes TSP, SO_2, NO_2, CO and O_3. Moderate correlations were found among the primary combustion pollutants. Using an analytic strategy that more finely controlled for time trends than did earlier approaches, effects were seen of either TSP or SO_2 considered alone, or in

combination with O_3 on mortality. Ozone had consistent effects on mortality, even following control for other pollutants. A less plausible association with lagged CO was also apparent in the data independent of TSP/SO_2 and ozone. The authors concluded that air pollution was associated with increased mortality during the years 1973-1988; significant effects were present for either TSP or SO_2,(considered as representing the complex of primary combustion pollutants), and for O_3.

Questions/Answers and Discussion

Substantial comments and questions that came from the attendees included the following. Dr. Pope was asked how epidemiologists select particular methods for their studies. He answered that the bottom line was the judgement of the principal investigator and his/her colleagues. A comment was made relating to Dr. Dockery's conclusion that acidity was not a likely contributor to the epidemiological associations. The commentor pointed out that the data on acidity are sparse and that summertime is best for looking for the effects of acidity. Similarly, it was pointed out that the absence of signal (in epidemiological studies) from large particles may be due to their not being measured as accurately as are small particles. Relating to the paper by Dr. Samet, two comments were offered. First, it was pointed out that day-of-the-week effects deserve additional consideration in epidemiological evaluations. Second, a comment was made that differences in indoor vs outdoor exposures also need more investigation. Finally, it was pointed out that carbon monoxide concentrations track black carbon concentrations in the air, implying that separating their effects is difficult.

In the general discussion, the question was asked as to why different epidemiological evaluations give different results. Dr. Samet responded that different investigators tease out different signals. Yet, he commented, that still one is left with an air pollution effect - for sure when TSP is considered, but sometimes yes and sometimes no for other pollutants. It was pointed out that singling out particles could be erroneous, and that the complex air-pollution mixture may be the real culprit. Other comments relating to epidemiological studies were made. The problem of looking for thresholds at low levels of pollutants, where random effects are possibly significant, was brought up. Also, the issue of the importance of identifying causes of death was mentioned. In this regard, it was offered that about 20% of the people dying in Philadelphia are autopsied, and that studies of these cases should be performed. Another comment pointed out that the best predictor of health effects might be the change in daily air-pollution levels, rather than the absolute levels.

Discussion relating to toxicology studies was less extensive. The question was asked: "Can (animal) models be developed for the very frail and susceptible people?" Dr. Schlesinger replied that such models are currently emerging.

A:sess1

Epidemiological Findings

Ursula Ackermann-Liebrich[A] and Douglas W. Dockery[B]
[A]University of Basle, Institute of Social & Preventative Medicine,
Steinengraben 49, 4051 Basle, Switzerland
[B]Harvard School of Public Health, 665 Huntington Avenue,
Boston, MA 02115, U.S.A.

This session focused on issues relating to the analysis of time series data in assessing the effects of particulate air pollution on daily mortality (presentations by Drs. Kazuhiko Ito, Suresh Moolgavkar, Kenneth Boucher, Laurence Kalkstein, and Douglas Dockery) and hospital admissions (presentations by Drs. Suresh Moolgavkar and Kenneth Boucher). While there are differences in effects reported, and differences in the interpretation of results, there is general agreement now on the analytic methods being employed in the analysis of these time series data. Moreover, there is a general consensus that the observed associations with air pollution cannot be explained by inadequate control of weather, and specifically the consideration of synoptic weather categories (presentation by Dr. Laurence Kalkstein), in the time-series analyses.

Recent studies have generally found lower effect estimates than those reported in the initial series of time series analyses. Sorting out the magnitude of the "true" effect remains controversial. Some argue that these low effect estimates are due to the more sophisticated analytic methods being used and the better control of potential confounding by weather and co-pollutants. Others suggest that these differences reported in the reanalyses of previously published data (presentations by Drs. Suresh Moolgavkar and Kenneth Boucher) may be due to over-control of long-term time trends and weather factors. Nevertheless, even in these reanalyses there are still positive, statistically significant associations observed with daily air pollution exposures. This suggests that there is a true underlying association with acute air pollution exposures. Differences in effect estimates between cities may represent true differences in exposure to the unmeasured specific characteristic of particulate air pollution exposure. The presentation by Dr. Douglas Dockery suggested that increased mortality in Philadelphia was specifically associated with fine particles ($PM_{2.5}$), and that this association was independent of the effects of other co-pollutants.

The strongest epidemiological evidence to date for an association between particulate air pollution remains the consistency of the observed associations by many investigators across a range of communities with varying climatic, cultural, and air pollution characteristics. Despite progress in understanding the epidemiology, the question remains open as to what specific characteristic(s) of the particles is (are) responsible for the observed associations.

a:sess2

Epidemiological Findings

Aaron Cohen[A] and Dane Westerdahl[B]
[A]Health Effects Institute, 141 Portland Street, Suite 7300,
Cambridge, MA 02160, U.S.A.
[B]California Air Resources Board, 2020 L Street, Sacramento, CA 95814, U.S.A.

Although the five papers presented in Session 13 addressed diverse aspects of the relation between particulate air pollution and respiratory morbidity, there were several unifying themes. Three studies examined the effects of particulate air pollution on the respiratory health of children, with a predominate emphasis on asthma. Children have been preferred subjects in studies of air pollution health effects both because of the enhanced sensitivity of their respiratory systems and because they are less exposed to potential confounding factors, such as cigarette smoking and polluted occupational environments. Asthma, particularly in children, is pandemic, but the etiologic role of ambient air pollution is controversial. Two studies addressed the critical issue of the chronic effects of long-term exposure to particulate air pollution, and presented new findings from two important, on-going prospective cohort studies. The impact of long-term exposure remains one of the outstanding areas in need of further research.

The studies of Dr. G. Hoek et al., and of Dr. J. Pekkanen et al., reported on the effects of short-term increases in particulate air pollution on peak expiratory flow rates (PEF) in asthmatic children, in the Netherlands and Finland, respectively. Both studies observed small decrements in PEF in relation to daily PM_{10} increases. The Finnish study was able to make separate estimates of exposure to primary emissions and resuspended road dust, and observed an apparent difference in the induction time for PEF effects with resuspended dust having a more immediate effect on PEF and primary emissions a relatively delayed impact.

Effects of long-term exposure to particulate air pollution in both children and adults were reported from separate prospective cohort studies. Dr. John Peters presented the results of cross-sectional analyses of 12 California communities conducted as part of California Air Resources Board 10-year prospective study of child respiratory health. He observed no apparent effects of lifetime PM_{10} exposure on pulmonary function, but reported that exposure was associated with a 5% increase in the prevalence of chronic bronchitis and with the number of school absences due to respiratory illness. An interesting methodologic finding was that analyses that characterized exposure at the community level failed to observe these associations, which only became apparent in analysis that used model-based estimates of lifetime exposure. Dr. Abbey reported the most recent findings from the Seventh Day Adventist Cohort study of non-smoking adults. Exposures to PM over approximately twenty years were associated with a 60% increase in the incidence of chronic productive cough, and there were weak indications of an effect of PM_{10}

exposure on the development of asthma. There was some suggestion that PM and ozone might interact to increase the rate of asthma occurrence, but interpretation was complicated because the results differed by sex, and the discussion following the presentation shed little light on the reason for the differences.

The remaining papers, by Drs. Yuanzhang Li and D. Roth, analyzed the relation between hospital admissions for cardiovascular and respiratory diseases and daily levels of particulate air pollution in a single U.S. city. Dr. Roth presented the results of 9,000 regression analyses of aerometric, meteorologic, and hospital admissions data, and reported that effects of PM_{10} on hospital admissions were not elevated consistently across all analyses. These findings were contrasted with earlier analyses that had shown an effect, though the previous analysts had specified an a priori interest in certain models and had therefore conducted a more restrictive set of analyses. Dr. Roth stated that he had been able to reproduce the original findings, but thought that his results suggested that the earlier findings were the result of random error.

In the general discussion period presenters and members of the audience discussed several broad issues that were raised by the papers. The impression that the apparent effects of long-term exposure on pulmonary function were either weak or non-existent prompted the question of whether the tests of pulmonary function employed, e.g. FEV_1, might not be sensitive to early chronic damage, and whether tests of small airway function, such as flows at low lung volumes, might not be better. Drs. Peters and Abbey were asked whether the results of their studies might be used to estimate directly the health benefits that have accrued from air quality regulation, given that these regulations have resulted in diminutions of ambient air pollution in California over the past decades. Dr. Peters responded tentatively that studies such as his might possibly allow such estimates.

a:sess13

Epidemiological Findings

Bart Ostro
California Dept. of Health Services, 2151 Berkeley Way,
Berkeley, CA 94704, U.S.A.

This session included several new epidemiologic studies relating particulate matter to mortality and morbidity. The preliminary analysis presented by George Thurston involved the association between PM10 and mortality in 9 U.S. cities. The aims of this work included the use of a consistent statistical approach for all of the cities, consideration of the influence of co-pollutants, and examination of factors that may influence the PM10 mortality association. Daily data for the period 1981-1990 were used in models that controlled for temperature and humidity, seasonality, time trends, and other pollutants. Among the important findings reported in this paper were: (1) the differential impact of same-day versus lagged temperature; (2) the consistent association between PM10 and mortality across the cities; (3) the sustaining of a PM10 association with morality after other pollutants were included in the model; and (4) the insensitivity of the results to alternative adjustments for seasonality. Regarding the latter, four options were considered including: a trigonometric fit, a 31-day filter of mortality, and two different LOESS (locally weighted moving average) fits. Additional analysis of this data set will seek to address the issue of the effect modifiers of the PM10-mortality associations.

The next paper (Charon Gwynn et al.) focused on air pollution and health effects in Buffalo, New York. In considering both mortality and hospital admissions, the researchers were able to check for coherency, i.e., the consistency of a pollution effect across multiple health outcomes. The findings indicated that both aerosol acidity, measured as H^+, and PM10 were associated with the health outcomes. The inclusion of the gaseous pollutants including ozone, carbon monoxide, sulfur dioxide and nitrogen dioxide did not effect the H^+ coefficients. These findings lend credibility to the hypothesis of an effect of airborne aerosols on mortality and morbidity, with minimal confounding by co-pollutants.

Kevin Fennelly and Bucher Bartelson presented results of an analysis on cardiopulmonary morbidity in Denver, Colorado. Specifically, daily data on hospitalizations for various cardiopulmonary diagnoses were examined for their association with both PM10 and carbon monoxide (CO). The findings indicated that using a single pollutant model, both PM10 and CO were associated with hospital admissions when a cardiac condition was listed as a primary diagnosis and a pulmonary condition was listed as a secondary diagnosis. There was no association when a pulmonary condition was not listed as a secondary diagnosis. In the multiple pollutant model, only PM10 was associated with cardiopulmonary admissions. However, additional analysis indicated that CO was associated with admissions for congestive heart failure among an elderly cohort. These findings generate support for the findings by other researchers of an association between

daily concentrations of particulate matter and either respiratory or cardiovascular mortality.

Joachim Heyder et al. presented findings regarding fine (< 2.5 μm) and ultrafine (< 0.1 μm) particles and exacerbation of asthma in Erfurt, Germany during the 1991/92 winter. During this period, 79% of the particles below 2.5 μm were smaller than 0.1 μm in diameter, but particles between 0.1 and 0.5 μm made up 82% of the mass. The daily correlation between fine and ultrafine particle concentrations was 0.51 thereby enabling some distinguishing between health effects of particles of different sizes. Using a sample of 27 moderate asthmatics, ultrafine particles were more strongly associated with decrements in peak flow than were fine particles. In addition, using 5-day moving averages of concentrations, both fine and ultrafine were associated with daily cough. These findings lend support for a role of both fine and ultrafine particles in the exacerbation of asthma and possibly for other respiratory effects. Additional research on the relative effects of particles of different sizes is warranted.

The paper by of Klea Katsouyanni et al. reported results of an analysis of air pollution and mortality among 10 European cities. These cities represented a wide range of demographic profiles, pollution concentrations and mixes, and meteorological conditions. The analysis used a standardized methodology across the cities and controlled for weather, seasonality and time trends. Associations were reported between PM10 and all-cause mortality in the Eastern European cities; but not in the Eastern-Central European cities included in the analysis. Black Smoke (BS), a measure of the blackness of the particles was also associated with respiratory and cardiovascular mortality. The use of a meta-analysis to pool the results across all of the cities indicated an association between mortality and sulfur dioxide, BS, and PM10 for all cities, all Western European cities, and all Central-Eastern European cities. Of particular interest, sulfur dioxide tended to have a stronger association with mortality than did the particle measures. However, the cities with the highest sulfur dioxide concentrations (i.e., those in Eastern and Central Europe) did not exhibit associations between that pollutant and mortality. This indicates that there might be greater measurement error at higher concentrations of sulfur dioxide, or that sulfur dioxide in these cities might be a better proxy for some other causal pollutant, such as fine or ultrafine particles, than is PM10 or BS. Further research on the association between these pollutants over time is warranted. In addition, investigation of differences in the underlying populations (Western versus Central-Eastern Europe), such a demographics, competing risks, and spatial distribution of population and air pollution monitors is warranted.

Toxicology

Richard B. Schlesinger
New York University Medical Center, Environmental Medicine, Tuxedo, NY 10987, U.S.A.

This session primarily examined PM components of potential interest in terms of health effects and biological effects of potential concern.

Andrew Ghio indicated that combustion of fossil fuels can result in the production of particles containing components which have the ability to complex transition metals. He noted that air pollution particles collected on filters did contain transition metals. It was suggested that such metals may cause oxidative stress in exposed cells.

Ann Aust showed that exposure of cultured human lung cells epithelial cells to standardized particles containing 3% iron (a model for urban PM) showed increased levels of ferritin, indicating increased iron mobilization.

Susanne Becker exposed macrophages (in vitro) to PM from three urban areas, to oil fly ash and to volcanic ash. The phagocytic ability of these cells was assessed to determine biological response to the particles. The urban particles affects the regulation of expression of certain receptors involved in phagocytosis of microorganisms and in cell to cell interactions. Different particles affected receptor expression in different ways.

James Samet exposed human airway epithelial cells to respiratory residual oil fly ash particles. There was a change in the synthesis of the bioactive mediator PGE2.

Kent Pinkerton exposed rats to sidestream cigarette smoke and examined Clara cells. He noted enhanced activation of P450 in these cells, especially at bifurcation areas.

a:sess4

Particle Deposition and Clearance

Gerhard Scheuch
Institute for Inhalation Biology, Robert Kochallee #6, D-82131 Gauting, Germany

The poster papers presented in this session were all related to the topic: Deposition and clearance of aerosol particles in the lungs. There were four papers related to modeling and two papers that concerned actual experiments.

The paper of William Bennett and K.L. Zeman presented experimental data on particle deposition in children (8-18 years old) during spontaneous breathing. The total deposition fraction, DF, was found to be independent of age and body height for 2 μm diameter carnauba wax particles; DF was in the order of 20% for children as well as for adults (19-35 years old). On the other hand, the dose per lung surface area was higher in young children than in adults, because of the smaller lungs in the children. These data are of use for estimating age-related risks associated with inhaling ambient particles.

The second experimental paper was from Thomas Hesterberg, W.C. Miller and G.A. Hart. This group measured the deposition and retention of synthetic fibers in rats. After a short-term inhalation of different types of fibers the animals were killed and the retained fibers characterized. Synthetic Vitreous Fibers (SVF) disappeared more rapidly from the lungs of the animals than did crocidolite asbestos fibers. The longer synthetic fibers appeared to dissolve faster and break more easily than shorter fibers. The conclusion seems plausible in that lower biopersistency and lower toxicity has been previously observed for the smaller SVF in relation to larger fibers.

Margaret Ménache presented information that showed that the particle inhalability is species dependent. For small laboratory animals, larger particles are less inhalable than for humans under the same experimental conditions. This result is important for understanding and interpretation species differences in exposure experiments.

In three papers a commercially available computer program (FIDAP) was used to simulate flow trajectories and deposition pattern in different airway models. With fast computers and this fluid dynamics program it should be possible to calculate sites of deposition of aerosol particles in the airways and to simulate the complicated flow fields in airway structures.

Bahman Ashgarian, L. Zhang and S. Anjilvel showed in their model calculations that the deposition was affected by the orientation angle of a second bifurcation in a double bifurcation airway cast. Lei Zhang and coworkers made a computer reconstruction of the central airways of a male rat. With these reconstructed

airways a flow simulation computer program can calculate flow fields and particle deposition efficiencies.

Ramesh Sarangapani and A.S. Wexler made a CAT (Computer aided tomography) scan reconstruction of the human nasal airways and used it for computer flow simulations. In addition, the calculated deposition pattern of inhalable particles under various breathing conditions were estimated by solving the equations of motion and thereby obtaining particle trajectories.

In the stimulating discussion, participants agreed that in future modelers and experimentalists should work together as closely as possible. Modeling efforts can offer much help for understanding experimental findings from particle deposition experiments, as well as help to solve open questions about deposition mechanisms. On the other hand, a computer model is only helpful when it can be compared to an experiment, and when the prediction in close agreement with the experimental results.

Additional discussion centered on important directions for future research. Among the needs were additional anatomical information on airways of laboratory animals and humans (especially children) so that variability in particle deposition could be modeled.

a:sess5

TOPICAL WRAP-UP

SUMMARY: MECHANISMS OF INJURY

Richard B. Schlesinger, Ph.D.

Department of Environmental Medicine
New York University Medical Center
Tuxedo, NY 10987

A problem in understanding the epidemiological findings of increased mortality/morbidity related to ambient particulate matter (PM) is the lack of biological plausibility for the observations noted in such studies. Papers presented in three sessions of the Colloquium attempted to provide some indication of possible mechanisms which could account for the health effects noted in population-based evaluations.

Three main questions were addressed in these sessions: 1) What are the potential constituents of ambient PM which could be responsible for adverse health effects; 2) Is there toxicological evidence that certain individuals may be more susceptible to effects of PM than are others; and 3) What are potential underlying mechanisms which could result in increased mortality/morbidity from PM? An approach used in a number of studies is exposure of animals or other biological assay systems to "real" PM, i.e., either actual ambient urban aerosols or model mixtures containing important components of ambient PM. Such an approach shows the realization that biological effects may actually be due to some mixture of "air pollution," rather than to one constituent of PM.

Physicochemical Characteristics of PM Which May Underlie Toxicity

The specific characteristics of PM which may be responsible for its biological effects involve both certain chemical species present in the aerosols, either in pure form or as a surface coating on other particles, as well as certain size characteristics of the aerosol itself. The role of these physicochemical characteristics in ultimate biological response has been examined *in vitro* using lung cell and tissue systems, as well as *in vivo* using laboratory animal models.

Materials present as a surface coating on other particles may become bioavailable upon deposition of the carrier particles within the lungs. Transition metals, such as iron, have been suggested to result in oxidative stress, due to their ability to participate in the production of reactive oxygen species via the Fenton reaction. The potential role of transition metals such as iron in biological effects due to PM is supported by some*in vitro* studies which have indicated that the toxicity of particles can be reduced by removal of associated iron prior to exposure of cells or tissues.

Another potential contributor to effects from ambient PM is acidity, which can be present either in pure droplet form or as a coating on other particles. Inhaled acid, generally in the form of acid sulfate, has be shown to result in alterations in mucociliary transport, alveolar macrophage function and airway reactivity in animal studies, and changes in pulmonary function in certain humans, notably asthmatics. Some studies have noted that acid as a surface coating produces biological responses at lower concentrations than if the acid was present in the exposure atmosphere as a pure droplet. Thus, surface coated acid may be more potent and could result in effects at concentrations closer to those noted in ambient air.

Another physicochemical characteristic of particles related to biological potency is particle size. For example, a study examining various size modes of ambient particles noted that than those <1.7 μm generally produced greater responses and more persistent effects than did larger particles.

A number of studies using particles having "low intrinsic toxicity" noted that biological responses were significantly enhanced when the particles were present as ultrafines, that is, having diameter less than 0.1 μm. Such particles appear to have greater inflammatory potential than those in larger size modes. The reasons for this are not clear, but may involve the fact that the smaller size particles have a larger surface area to volume ratio, so they may serve as more effective carriers of adsorbed/absorbed materials, such as metals, acids or even peroxides. Furthermore, for a given mass concentration of a chemical species, there is a greater particle number concentration in an ultrafine aerosol than in a fine aerosol; thus, if particle number is a factor in toxicity, the smaller particles may be more potent. Number concentration has been suggested to play a role in response to some materials such as acid aerosols. One study has shown that there may actually be a threshold level for both number concentration and mass concentration, at least for acid coated particles, in eliciting biological responses.

While studies have been attempting to tease out certain components of PM which may be responsible for its biological effects, what is becoming clearer is that such effects may be influenced by exposure to mixtures of PM with other materials, such as antigens or ambient pollutant gases. Furthermore, certain characteristics of PM may be important in any interaction with other components of the exposure atmosphere. Thus, for example, rats exposed to atmospheres containing sulfuric acid and ozone showed an interactive response from these two materials only when the acid was present as ultrafine particles and not when it was present at the same mass concentration but as larger, fine mode particles.

Potentially Susceptible Populations

Epidemiological studies provide some evidence that certain components of the general population may be more susceptible to the adverse effects from ambient PM. Toxicological studies are beginning attempts to examine this using animal models of potentially susceptible individuals.

In one study, older rats were exposed to a model atmosphere containing certain components of ambient PM. Biological effects were noted in these animals, but not in younger rats exposed to the same materials. Another study exposed "health compromised" rats to concentrated ambient urban aerosol. The animals had either pulmonary hypertension induced by exposure to monocrotaline or chronic bronchitis induced by exposure to sulfur dioxide. Increased mortality was noted in the compromised animals compared to normal rats exposed to the same atmosphere. Thus, these initial studies suggest that healthy hosts may be able to handle the insult of exposure to PM atmospheres, while those with pulmonary function may not.

It is possible that altered dosimetry in health compromised animals may play some role in any increased sensitivity. For example, chronic obstructive pulmonary disease may result in an altered pattern of particle deposition, and areas of enhanced PM concentration in certain regions of the lungs compared to normal individuals. This could result in exaggerated biological responses.

Mechanisms Underlying Toxicity of PM

In a talk at this Colloquium, Dr. Mark Utell listed four potential underlying mechanisms to explain the increased mortality/morbidity noted in populations studies as related to ambient PM. These were: 1) pulmonary edema; 2) increased acute respiratory infection; 3) exacerbation of chronic respiratory disease; and 4) cardiac arrhythmia. There is beginning to be some toxicological evidence that potential components of PM may elicit these mechanisms.

The production of pulmonary edema by exposure to PM could result in decreased oxygen transport in the lungs. Size fractionated ambient air particles instilled into rat lungs produced edema, with the most progressive response due to the smallest particle fraction used, i.e.,<1.7 μm. Edema was also noted to occur in some of the health compromised animals, noted above, which were exposed to concentrated ambient PM.

In terms of increased acute respiratory infection, some ambient PM, as well as acid sulfates, can affect macrophage phagocytic activity, an important component of the lungs' antimicrobial defense. There is also some direct evidence for a reduction in antimicrobial activity of these cells due to exposure to acid sulfates. Such a reduction could result in an increased incidence or virulence of acute infection, which may be more life-threatening in individuals with already compromised cardiopulmonary function, such as those with pre-existing chronic lung disease, or the elderly, who may already have somewhat reduced immune competence.

Some studies suggest that ambient PM or components can exacerbate existing chronic pulmonary disease. Exposure to concentrated ambient PM in compromised rat models noted above resulted in production of inflammation and bronchoconstriction. Exposure to a model of PM components, namely residual oil fly ash (ROFA), produced a strong inflammatory response, which could be more life-threatening for people with

preexisting lung disease or the elderly due to enhanced production of inflammatory mediators. Exposure to acidic aerosols has been implicated in production of airway hyperreactivity (a hallmark of asthma), alterations in bronchial mucociliary clearance and increased numbers of mucus secreting cells in small airways (a hallmark of chronic bronchitis).

One of the main problems in determining mechanisms underlying health effects from PM is that some of the responses are clearly systemic, such as cardiac arrhythmia. To date, there is no direct toxicological evidence that exposure to PM can produce systemic effects. However, some suggested pathways for systemic effects from respiratory tract exposure to PM have been proposed. For example, systemic effects may result from PM-induced changes in the production of cytokines in the lungs, and these cytokines may enter systemic circulation. Systemic effects may also result from effects upon the central nervous system following PM-induced stimulation of the lung's nervous system.

Conclusions

At the First Colloquium in January, 1994, speculation was rampant concerning biological plausibility underlying the PM epidemiological database. At this point, two and a half years later, there are much new data to indicate potential constituents of PM which may be responsible for PM related adverse health effects. Clearly, certain chemical species and certain size characteristics are likely important in this regard. Furthermore, there is support that PM appears to affect compromised individuals to a much greater extent than normal individuals, perhaps by inducing an extra burden of stress which the former are unable to handle. While many studies examining mechanisms of injury used nonphysiological methods of administration and/or very large doses of materials, there is clearly the beginnings of an understanding of potential components which may be involved in PM effects, and of mechanisms underlying effects in susceptible populations. Furthermore, there is also the beginnings of an acceptance that biological effects may be due not to one component of PM, but result from exposure to some pollutant "mix" involving PM.

C. Exposure Assessment and Sampling; Total Exposure

Exposure Assessment & Sampling

Beverly Cohen[A] and Constantinos Sioutas[B]
[A]NYU School of Medicine, Long Meadow Road, Tuxedo, NY 10987, U.S.A.
[B]Harvard University, 665 Huntington Avenue, Boston, MA, 02115, U.S.A.

Five innovative and interesting research papers were presented at this session. Two of the papers detailed technological advances for studying ambient particulate matter, two were field studies, and one highlighted the significance of electrostatic charge, an important but neglected properly of ambient particles.

P.K. Dasgupta described an automated particle collection and analysis system that provides nearly real time measurements of ambient aerosol acidity. This system utilized an innovative supersaturation system to produce condensational growth of ambient fine and ultrafine particles. The particles are steam-saturated and led through a cooling maze where the supersaturated particles are collected. The soluble components of the collected condensate flow are analyzed via ion-chromatography (IC). Acidity is determined from the difference between the total cation and anion equivalents. The sampling time resolution depends on the duration of the IC cycle and was about 8 minutes from the system presented here. Pre-collection of gases by a diffusion denuder with a flowing liquid substrate also allows separate, real time, analysis of ambient gases via an independent IC. Detection limits are in the range of a few ng/m^3 of strong acid.

C. Sioutas reported the development and testing of an ambient fine and ultrafine particle concentrator that utilizes a series of virtual impactors to concentrate ambient fine ($0.1 < dp < 2.5$ μm) and ultrafine ($d < 0.1$ μm) particles. Entry to the concentrator is limited to fine particles by a 2.5 μm cut-size pre-impactor. The concentrator was developed for inhalation exposure studies and delivers the aerosol at an enrichment of 9.5 and 25, for two and three stage systems. In addition, he described a system designed to grow ultrafine particles to micrometer size. The enlarged ultrafine particles are then effectively concentrated by a virtual impactor.

A comprehensive ongoing monitoring and health effects study initiated in July 1994 in Spokane, WA was reported by J. Koenig. Ambient monitoring at a residential site, and an industrial site, has begun to sample PM10, PM2.5 and PM1.0, condensation nuclei concentration, SO_2, No_x and CO. A chemical species vapor and particle sampler is also deployed. Preliminary data indicate that windblown dust enhances both the fine and coarse fractions of the Spokane aerosol, and that the concentration of condensation nuclei is twice as high in winter than summer. In the future, the measured parameters of the ambient air will be examined in conjunction with meteorological data to support an extensive panel of measures of health status.

Results of a 1992 summer field study of particulate mass, sulfate, sulfate dioxide, and ozone concentrations in metropolitan Philadelphia were presented by J. Zhang. Diurnal patterns demonstrated the coarse particle concentrations peaked early in the day (6 to 7 AM), while in the afternoon PM10 concentrations climbed as a result of increased fine particle concentration (PM2.5). The work also established a correlation between sulfate at time t and SO_2 at t-7 hours.

The last paper of the session, presented by B. Cohen reported that ambient airborne particles are commonly charged and the electrostatic charge on particles is an important determinant of how efficiently they deposit in the respiratory tract. To estimate the charged fraction of ambient ultrafine ($d < 0.2\ \mu m$) particles, the number that are naturally charged was compared with the number charged when an equilibrium state is established experimentally. The measured charged fraction was quite variable and depended on particle size, but commonly exceeded the equilibrium number by 50% or more. Thus 80 to 90% of the ambient particles carried one or more charges. This indicates that electrostatic charge effects must be considered when examining the physical behavior of ultrafine ambient particles.

a:sess16

Exposure Assessment and Sampling

Robert F. Phalen
University of California, Community and Environmental Medicine,
Irvine, CA 92697-1825, U.S.A.

Five platform papers on diverse subjects were presented, followed by a focussed discussion in which the presenters and several other attendees addressed the following question: "What are the major lessons and unresolved issues?" The remainder of this summary will briefly cover the content of the formal presentations, summarize the focussed discussion, and present the major issues that require further research for their resolution.

Summary of Papers

The first paper, presented by Frederick W. Lipfert (environmental consultant) and coauthored by Ronald E. Wyzga (Electric Power Research Institute), was entitled; "Simulation Studies on the Effects of Exposure Error on Environmental Epidemiology." The paper described distributions of personal, indoor and outdoor exposures of populations in cities of various sizes, along with methods for simulating the influences that spatial and temporal variability can have on epidemiologic study outcomes. Conclusions were drawn, resulting from exploratory simulations, to project how the use of personal exposures, in place of ambient exposures, would influence epidemiologic outcomes. A major prediction was that threshold concentrations for health effects could be obscured by errors in individual exposure assessments, resulting in an apparent linearity in exposure-effect relationships, when ambient data are used as a surrogate for personal exposure.

The second paper, "An Evaluation of PM_{10} Measurements Made by Tapered Element Oscillating Microbalances (TEOM) in Southern California," was presented by Richard Reiss, and coauthored by Paul T. Roberts, Frederick W. Lurmann and David Wright (all of Sonoma Technology, Inc.). This instrument is currently providing hourly ambient PM_{10} data at 13 sites as part of the ongoing Southern California Children's Health Study to characterize daily exposures. The TEOM sampler is operated at 50°C to eliminate problems associated with collecting water; however, the use of this temperature may also lead to volatilization of nitrates and some organic species. Data were presented which provided several comparisons of TEOM and nearby (within 10 km) High Volume (Hi Vol) samplers in cities with differing air-pollution mixtures. The TEOM-measured PM_{10} was frequently lower than that indicated by the Hi Vol samplers; the difference was greatest in the most polluted cities. Differences in PM_{10} correlated with differences in nitrate concentrations, suggesting that volatilization of ammonium nitrate occurred. Also, evidence was presented that other volatile pollutants, such as organics in wood smoke, etc., may be undersampled by the TEOM. Regression equations were presented to provide the necessary adjustment of TEOM data to Hi Vol results.

The third paper, "The Use of a Centrifugal Concentrator in Ambient PM_{10} Toxicology Studies," was presented by Terry Gordon and coauthored by C.P. Fang, H. Gerber and Lung Chi Chen (New York University and Gerber Scientific). The Gerber Concentrator,

tubular in shape, uses suction through a spinning porous inner tube to pull the air away from the particles traversing the annular space. At the outlet of the device the annular space is enriched up to 20-fold in fine particles. Ultrafine aerosols are neither concentrated nor lost, while coarse-modes are lost due to impaction. The concentrator is used for supplying animal exposure systems with concentrated ambient PM_{10} in toxicology investigations.

The fourth paper, "Fine Particulate N-nitroso and Nitrite Organic Compounds in the Atmosphere," was presented by Yiming Ding and was coauthored by W. Cui, Milton L. Lee and Delbert J. Eatough (all of Brigham Young University). The purpose of this investigation was to provide both phase-distribution and particle-size related information on labile and semi-volatile nitrogen-containing compounds in the ambient air of Provo, Utah. A diffusion denuder and a variety of analytical techniques were applied to the problem. It was found that the majority of N-nitroso and nitrite organic compounds which are present in fine particulate matter are lost during conventional particle sampling. Also, the concentrations of these fine-particulate components are comparable to their concentrations in the gas phase of ambient air.

The final paper, "Aerosol Time-of-Flight Mass Spectrometry: A New Method for Performing Real-Time Characterization of Aerosol Particles," was presented by Christopher A. Noble and coauthored by Kimberly A. Prather (all of the University of California, Riverside). Aerosol time-of-flight mass spectrometry (ATOFMS) is a new real-time technique which provides chemical composition data for individual particles of known aerodynamic diameter. Aerodynamic particle sizing is performed by a dual-beam laser timing system which preceeds a time-of-flight mass spectrometer in the instrument. ATOFMS has been used to provide size-resolved chemical analyses for several aerosol systems including ambient air pollution, environmental tobacco smoke, automobile emissions and laboratory aerosols. For ambient aerosols, time-resolved size distributions for various chemical species were presented. It was proposed that this level of detail is useful in developing an understanding of the health effects of specific components of ambient particulate material.

It was clear from the formal presentations described above that a substantial variety of sophisticated analytical techniques for the study of ambient air-pollution are emerging. It was also clear that such techniques have not been adequately incorporated into the epidemiologic or toxicologic investigations that have been conducted, or are currently underway. This is not surprising, as the techniques presented in this session are new and, in many cases, expensive.

Focussed Discussion

In addition to the presenters, several other well-known scientists were in attendance at the session. In order to make use of the assembled expertise, attendees were challenged with defining what was learned, and with identifying the major unresolved issues with respect to sampling for exposure assessment.

Susanne V. Hering (Aerosol Dynamics, Inc.) pointed out that currently-used sampling methods undersample semi-volatile aerosols, resulting in substantial losses (50% or

more) of potentially-important chemical species. This has produced a focus on the distinction between what is collected on filters (for compliance purposes), as opposed to ascertaining what is in the air as it is being breathed. There is a need to focus on the information that is required in health-effects studies. In addition, the loss of volatile and semi-volatile air pollutants when using conventional sampling techniques affects the very definition of "fine particles". The current definition is dependent on delayed chemical analyses performed on residues on filters, which is not equivalent to what is being inhaled. What is currently being measured are therefore "surrogates" for the actual pollutants. Are these surrogate measurements fortuitously valid for the epidemiologic investigations? Delbert J. Eatough (Brigham Young University) pointed out that the very chemical components that are undersampled using current techniques are possibly the more toxic species in the atmosphere. This undersampled portion certainly includes short-lived chemical compounds such as reactive oxygen species, in addition to semi-volatile nitrogen-containing compounds and a variety of reactive organics.

The question of what should be detected and quantified in outdoor and indoor air samples was raised and discussed. Should everything present in the air be analyzed? Is this possible? It was suggested that the sampling characteristics of the human respiratory tract should be considered in designing environmental sampling devices. It was also suggested that selected cities should be identified for more intensive sampling (based on epidemiologic study strategies).

Other insights regarding environmental exposures were offered, including the following. At a relative humidity of 70%, about 50% of the ambient aerosol is water. The presence of ammonia can decrease losses of some species from filters. In the eastern U.S., sulfate is perceived as a current problem; however, if sulfates are controlled, nitrates may emerge as a new health-related pollutant in that region. Currently, ASHRAE (American Society of Heating, Refrigerating, and Air-Conditioning Engineers) is struggling with similar issues in sampling indoor air for relevance to human health; communication with this organization was recommended.

Major Unresolved Issues

In summary, the following major exposure issues are in need of resolution:

* What are the most important chemical species toxicologically? When these have been identified, improved sampling methods can be devised and utilized to support the health-related studies.

* How should "particulate" be defined? Does the definition require specification of some standardized equilibrium conditions (with regards to temperature & humidity for example) in order to fix the volatile constituents?

* How can very short-lived species be sampled and analyzed under ambient conditions? This is particularly relevant if reactivity is a major toxicity-related property.

* How does the human respiratory tract selectively sample the myriad chemical components present in the atmosphere? Major uncertainties exist for semi-volatile compounds and for pollutant mixtures.

* How can new, more sophisticated (and currently more costly) sampling techniques be made available to those studying health effects? It is recognized that widespread sampling for compliance with ambient air quality standards will not require the same level of sophistication that is needed for sampling in epidemiologic investigations.

* What are the effects of using average ambient sampler data, rather than personal exposure data, on the outcomes of epidemiology investigations?

a:sess17

Total Exposure - Indoor and Outdoor Air in Residential and Occupational Settings

Joan M. Daisey[A] and Jeffrey S. Lee[B]
[A]Indoor Environment Program, Energy and Environment Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720
[B]Rocky Mountain Center for Occupational & Environmental Health, Dept. of Family & Preventive Medicine, University of Utah, Salt Lake City, Utah 84112

Abstract

The concept of total exposure - the sum of exposures at home, in the workplace, in other indoor and in outdoor settings, and in transit - is being used increasingly by the exposure analysis community to better understand the major and minor contributors to pollutant exposures of the population. In order to better understand the relationship between exposures to outdoor particulate matter (PM) and observed adverse health effects, the relative contributions of various exposure settings to total exposure must be taken into account. This will also provide a more scientifically defensible basis for the development of effective control strategies and policies aimed at reducing these effects. This paper summarizes research findings on PM exposures presented at the 2nd Colloquium on Particulate Air Pollution and Health and identifies several key research issues related to PM exposures and health effects.

Recent Research Findings Reported at the 2nd Colloquium

Although statistically significant relationships have been found between particulate matter (PM) measured at central outdoor monitoring sites and mortality and morbidity, the *total* exposure of an individual to airborne particulate matter (PM) is determined by the sum of the exposures experienced indoors at home, at work, in transit and in other indoor and outdoor locations. The relative contributions of outdoor PM and of other sources of PM to total exposures and related health effects are not well understood. A number of previous cross-sectional studies of population exposures to airborne particulate matter had suggested that there was only a very weak correlation between measurements of PM made at a central monitor with personal monitors. This was puzzling in view of the results of the epidemiological studies linking outdoor PM measurements with mortality and morbidity.

At this Second Colloquium, N. Janssen and her colleagues (1996) presented the results of a study of the relationships between PM_{10} personal exposures and PM_{10} measured in the ambient atmosphere at a central location *within* (i.e. over time for individual subjects) rather than across subjects. These investigators found very good correlations between personal and ambient measurements for both adults ($r = 0.71$) and children ($r=0.73$) when days with exposures to environmental tobacco smoke were excluded. For a smaller set of subjects for which personal and outdoor measurements were made of fine particles ($D_{50} \leq 3\ \mu m$) (PM_3, even higher correlations were found between personal and ambient measurements of PM_3) ($r=0.91$) over time when days with exposures to environmental tobacco smoke were excluded. For the PM_3, the average difference between personal and outdoor measurements for the children was only 5 $\mu g/m^3$ after excluding days with exposures to environmental tobacco smoke.

S. Hering and E. Avol (1996) reported on measurements of the indoor to outdoor ratios (I/O) for fine particle mass ($D_{50} \leq 2.3\ \mu m$) ($PM_{2.3}$), inorganic ions (sulfate, nitrate, and ammonium), and gaseous nitric acid in 12 houses in southern California using a new low-air-flow sampler. The I/O ratios for sulfate, which originates from outdoor air, ranged from 0.6 to 0.8 for air-conditioned houses, and from 0.9 to 1.0 for other houses, suggesting high penetration of outdoor particles into the residences. The I/O ratios for

$PM_{2.3}$ mass and nitrate ion were more variable and generally greater than one, indicating that there were contributions from indoor sources to $PM_{2.3}$. Nitric acid concentrations were consistently lower in indoor than outdoor air. In the home with a smoker, indoor $PM_{2.3}$ was five times higher than outdoor $PM_{2.3}$.

These two papers both indicate that outdoor fine PM effectively penetrates into the buildings in which children and adults spend most of their time, i.e., 70% in homes, 15-20% in workplaces and schools. These findings are consistent with some other recent reports (Thatcher and Layton, 1995; Wallace, 1996) indicating that the fine particles penetrate residential building shells with an efficiency close to 100% in many houses. Once inside the building, PM deposits on indoor surfaces (because of convective air flows and high surface to volume ratios). Thus, measured I/O ratios are often less than one for PM and PM components of outdoor origin.

Brauer, *et. al.* (1996) reported the results of using a nephalometer for continuous monitoring of PM to estimate contributions of smoking and cooking to 24-hour time-integrated total exposure measurements. The nephalometer was calibrated against various source emissions. Continuous measurements were made in restaurants, with and without smoking permitted, and in residential kitchens. Cooking in a home kitchen was estimated to contribute <1 to 8 $\mu g/m^3$ to total personal exposure over a 24-hour period. Exposures to PM from dining in non-smoking restaurants and in restaurants with unrestricted smoking were estimated to contribute 1-3 $\mu g/m^3$ and 1.5 to 10 $\mu g/m^3$, respectively, to total PM exposure measured over a 24 hour period. Thus, PM from indoor sources and activities can make significant contributions to total PM exposure.

The results of the epidemiological studies on mortality and PM have raised questions concerning the exposure periods and exposure locations of affected individuals. Since the exposures immediately prior to death may occur in hospital settings, exposure to PM in hospitals is of interest. Lillquist, *et al.* (1996) reported on the correlations between PM_{10} measured indoors in 3 hospitals, outdoors on the roofs of the hospitals and outdoors at a central location. The purpose of this work was to determine if outdoor PM monitors could be used to estimate indoor PM_{10} exposures in hospitals and whether PM_{10} measured in a single indoor location in a hospital could provide a good estimate of indoor concentrations and exposures. In general, the concentrations measured at the central monitor were higher than those measured at the rooftop sites. Indoor concentrations were generally lower than those measured outdoors. This is probably due to the HVAC (heating, ventilating, and air-conditioning) systems in the hospitals which typically filter the intake air. Large variations in PM_{10} concentrations were observed within and between hospitals, suggesting that indoor sources and differences in filtration efficiency were significant factors in determining the indoor measurements. For these 3 hospitals, the investigators concluded that PM_{10} at different indoor locations could not be predicted by one central outdoor PM_{10} monitor. Because of the common use of centralized HVAC systems in most hospitals, the conclusion of this study, that PM_{10} at different indoor locations cannot be predicted by one central outdoor PM_{10} monitor, is likely to apply to many other hospitals.

The papers on total exposure presented at the Colloquium, taken together with other recent studies, have provided experimental evidence that, for residential buildings, outdoor PM monitors for accumulation mode PM probably provide reasonably good estimates of the exposures of individuals to outdoor accumulation mode PM because of the high degree of penetration of these particles into such buildings. For buildings with HVAC systems and filters, such as hospitals and office buildings, penetration factors are likely to be much lower, with consequently lower exposures to outdoor PM. Experimental evidence was also presented at the Colloquium to show that indoor sources of particles, e.g., environmental tobacco smoke, cooking, resuspension of deposited dusts, can contribute significantly to *total* PM exposure. Occupational exposures in certain industries may account for the majority of any one individual's exposure.

Occupational exposures may commonly reach levels in excess of 1 mg/m^3 given that the OSHA standard for total dust is 15 mg/m^3; the current ambient standard for outdoor PM_{10} is 0.24 mg/m^3.

Some Exposure Analysis Research Issues

The papers presented at the Colloquium, taken with results of other recent research, have provided important advances in our understanding of exposures to outdoor PM_{10} and $PM_{2.5}$ for populations which spend most of their time indoors. However, a number of important scientific issues regarding PM exposures still remain if we are to fully understand the health effects of exposures to airborne particulate pollutants. Among these are:

What percentage of mortality and morbidity cases have significant exposures to indoor PM that might make some of this population more susceptible to adverse health effects from outdoor PM? How can we appropriately account for these other PM exposures in epidemiological studies?

It is clear that outdoor ambient and indoor PM sources at home, at work and in other microenvironments contribute to total PM exposures. The adverse health effects from exposures to many indoor PM sources are very similar or identical to those due to outdoor PM. For example, the relative risk of heart disease from exposures to environmental tobacco smoke is about 1.5-1.7 (Steenland, 1992; Wells, 1994). Twenty-five percent of the U.S. population smokes, so exposures to ETS are widespread (Jenkins, *et al.*, 1992). An analysis by Ostro (1989) suggests that ETS exposures contribute additively to outdoor PM-related morbidity. Exposures to certain indoor bioaerosols, such as house dust mite allergen, animal dander, and molds can cause asthma attacks and hypersensitivity pneumonitis (Samet, *et al.*, 1988). Indoor exposures to bacteria and viruses can cause infectious diseases, such as Legionellosis, and even death (Samet, *et al.*, 1988). Thus, some part of the adverse health effects attributed to exposures to outdoor PM might be due to or mediated by the contributions to total exposures from indoor sources and occupational exposures. A better understanding of the contributions of indoor, outdoor and occupational exposures to total exposure and to adverse health effects is needed for the population in order to make policy decisions that are effective in reducing adverse health effects.

Are exposures to ultrafine particles causing or contributing to the adverse heath effects attributed to PM mass?

At the 2nd Colloquium, research results were presented concerning the toxicological effects of ultrafine ($\leq$ 0.1 μm) PM (UFPM). These gave reason to suspect that exposures to the UFPM from outdoor air might contribute to or even be the causative agent for some of the observed adverse health effects due to PM. However, we have little or no information on the exposures of the population to UFPM. We also lack measurements of UFPM in outdoor air and information on their penetration into indoor environments that would allow us to estimate such exposures. Further, UFPM is not a measurement of lung deposition (or retention), thus adding to the difficulty of establishing relationships with health effects.

How do the relative proportions of PM and other air pollutants change once they have infiltrated into the indoor environments in which the population spends about 90% of their time?

The epidemiologists and toxicologists are beginning to investigate the effects of certain co-pollutants, such as ozone and CO, on responses to PM exposures. The penetration and subsequent depositional losses of these co-pollutants in indoor environments differ from those of PM. For example, the penetration of outdoor CO, which is very unreactive chemically, into indoor environments is 100%, and there are no indoor depositional losses. Indoor sources may also contribute to total exposure for some of these co-

pollutants such as CO. For ozone, depositional losses to indoor surfaces are highly variable and not well understood. Thus, the proportions of these two pollutants relative to PM in indoor air, where most of the population exposure occurs, can differ significantly from what is measured in outdoor air, thus confounding epidemiological studies based on outdoor measurements.

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D. Other Commentaries

CRITICAL DETERMINANTS OF RESPONSES IN HUMAN POPULATIONS

By: Dr. David V.Bates

May 3rd 1996

It is my view that the clinical credibility of the epidemiological findings is rather stronger than we have so far heard in this Symposium; the reasons for this are as follows:

1. People with COPD of any kind have significant nonuniformity of gas distribution within the lungs; hence the overventilated part of the lung will receive a higher dose of any respirable material. A bronchiolitis induced in the well ventilated part of the lung in such patients is likely to lead to hypoxemia very quickly.

2. Failure or incipient failure of the left ventricle produces pulmonary hypertension on exercise. Any inhaled material which can cause inflammation or edema in the lung is likely to lead to hypoxemia which would be a serious consequence in such an individual.

3. The interactions between the heart and lung when either organ is close to failure is very complex, but very real in actuality.

The results of Fenelly's work in Denver, and of Godleski's at Harvard, in very different fields of study, presented at this symposium, are both relevant to these considerations. In my view the "total package" of information we now have means that the clinical credibility of the epidemiological findings is substantially advanced.

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Comments by Wayne Leipold on 2nd Colloquium on Particulate Air Pollution & Health held at Park City, UT May 1-3, 1996

The type of work being performed by the scientific community needs to continue, but that it should not be forced to fit into a box whose shape and size is defined by the need for a compliance standard. In order to obtain sound science regarding the causes of mortality and morbidity, the scientist must be able to examine all of the characteristics of exposure, be it to liquids, gases or solids. However, for compliance purposes a very specific set of conditions must be enumerated. An example is the definition of a particulate and the test method in a NSPS standard (40 CFR 60).

Because the type of test designed for measuring compliance may not yield the type of data required by the epidemiologist, the compliance method should be simple, straightforward and inexpensive so that money is left in budgets to obtain data for epidemiological purposes. Although a seven day average sample from a high volume or dichotomous sampler would be sufficient for compliance purposes, it would not be useable for medical purposes and other sampling is required to fill the void. One example would be the use of a Beta gauge sampler with two substrates (teflon and quartz) which would allow XRF, carbon and other analyses to be performed on samples collected using shorter time frames. This latter category of instruments should not be used for compliance unless the measurements are averaged over the same time period and corrected for biases caused by the different sampling techniques.

Additionally, as we tend toward smaller and smaller mass measurements (as the size fraction decreases), it is critical that standardized procedures be employed which minimize errors due to mishandling filters, weighing errors, intrusion of particles, etc. By the same token, sensitivity analysis for the effects of errors in filter weights should be conducted by statisticians so that the possibility of a false conclusion can be noted or addressed.

RE: Comments on the 2nd Colloquium on Particulate Air Pollution & Human Health.

There was much interest at this Colloquium in assessing whether material progress has been made since the last Colloquium, and with recent initiatives, in establishing particulate air pollution as a causal risk factor for morbidity and mortality. Careful examination of the methods employed in the Philadelphia analysis and similar studies has presumed that resolving controversy over modeling issues is necessary for conclusions about causation. While Poisson regression of ecologic time series data is becoming quite a refined tool, it is not quite the right tool. Despite the sophistication of analysis of an ecological study, its limitations for causal inference are well established (notwithstanding recent attempts at rehabilitation of its reputation): the ultimate issue is that there is no guarantee in the ecological study design that those who experience endpoints are those who are also exposed to high levels of particulates.

In addition to the logical limitations of the ecological approach for conclusive assignation of causation, insufficient respect for other epidemiologic and statistical principles may continue to impede its utility. The magnitude of relative risks may be altered by inaccuracy in exposure measurement (bias away from the null! [1]) and outcome specification (attenuation bias). Moreover, it is important to the field to fully appreciate how differential mismeasurement among covariates might introduce a systematic bias sufficient to account for the small relative risks seen for particulates [2,3] in all studies to date.

While much hard work has gone into making the best of available data for implicating particulates as a cause of death and disease, only the very daunting task of obtaining individual level data measured with a minimum of error will suffice for drawing valid conclusions about causality. This calls for resources being devoted to developing and implementing the use of specific and validated endpoints, accurate and total exposure measurement, in a variety of potentially susceptible populations—even at the expense of continued focus on reconciling ecologic time series analysis methodology.

Drew Levy—Department of Epidemiology
University of Washington, Seattle, WA 98195

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What Has Been Learned Since the First Colloquium?
(Responses to the Colloquium Summary (Inhal Tox. 7:ix-xiii, 1995))

Frederick W. Lipfert, Environmental Consultant, Northport, NY 11768

1. **Are the time-series associations between mortality and PM_{10} robust?** (The 1995 Summary said: on the whole, yes.) While it can not be proven that PM_{10} is not associated with premature mortality, it has been shown that PM_{10} is not the only air pollutant so associated. All particle sizes except (TSP- PM_{10}) and all gaseous criteria pollutants have now been implicated.
2. **Can any common confounder be suggested?** It is not necessary that a confounder be "common". However, the 1995 Summary did not mention CO or NO_2, which are ubiquitous wherever fuel is burned; thus the issue remains. In addition, confounders are likely to differ by season, disease, and age.
3. **Why is cardiovascular (CV) mortality implicated?** (the 1995 Summary proposed no "convincing explanation"). An obvious response is the inclusion of CO as a co-pollutant. It should also be noted that CV mortality is not only "implicated"; it dominates total nontraumatic mortality.
4. **Is there convincing evidence of other effects of PM_{10}?** Yes, but none of these effects are unique to PM. CV hospital admissions are associated with CO; respiratory admissions with ozone. Lung function responses to PM are weak.
5. **Is an understanding of mechanisms necessary?** (1995 Summary: qualified yes.) Given the new findings on pollutant collinearity and recent toxicological findings, specific diseases should be linked with specific pollutants to establish biological plausibility.
6. **How does the composition of PM_{10} vary geographically?** Substantially. This is still the case and argues strongly that the premature mortality may not have an unique pathological aetiology.
7. **Might the active particles be submicron in size?** The 1995 Summary gave four supporting reasons:

    a. smaller particles are more likely to penetrate into the deep lung. Response: This might be a better rationale if the end point were chronic lung disease; it is difficult to make the case for strokes and sudden death heart attacks.

    b(1). similar indoor and outdoor concentrations. Response: it has been shown since 1994 that particle penetration into buildings is independent of size (for $d < 10$ um). Part of the reason for similar indoor and outdoor concentrations is the presence of indoor sources; however, individual personal exposures are poorly correlated with ambient data.

    b(2). Various correlations are higher for small particles. Response: this is the result of low concentrations and poor precision for the measurement of CP (only 10% of the sampled flow is used for CP.)

    c. Enhanced toxicity with very small (i.e., ultrafine [UF]) particles. Response: it remains to be shown that UFs can survive long enough outdoors or to penetrate buildings sufficiently to result in substantial personal exposure. Much of the health evidence for UF was obtained with particle types not found in the ambient.

    d. Higher personal exposures to PM_{10}. Response: Personal exposures to PM seem to behave similarly for both PM_{10} and $PM_{2.5}$ in that neither is correlated strongly with their respective ambient measures.

8. **What do we know about the effects of small particles from animal models?** None of the 1995 Summary's rationales seems particularly applicable to CV responses in humans at typical urban concentrations.
9. **Future animal studies.** There seems to be no special reason to limit such studies to PM; what is needed is a model for the endpoint (acute mortality at low concentrations), i.e., a "sick human" animal model. Then the model could be tested against various pollutants and particle sizes.
10. **Future epidemiological studies.** The ideas proposed by the 1995 Summary appear to deserve support, but little or no progress has been made on them in the U.S. since they were proposed.

Summary Comments on the 2nd Colloquium on Particulate Air Pollution and Health

Frederick W. Lipfert, Environmental Consultant, Northport, NY 11768
Ronald E. Wyzga, Electric Power Research Institute, Palo Alto, CA 94303

Occasionally a new or previously overlooked technical issue appears with such far-reaching implications that it requires reconsideration of all previous thinking on the topic. Exposure error is such an issue, even though the Colloquium appeared to remain largely indifferent to it. Advocates of specific agents as the "silver bullet" (i.e., $PM_{2.5}$, H^+, Fe^{++}, ultrafines) continued their advocacy without considering actual exposures and the types of errors incurred by using ambient data instead. Since our paper was the only one to consider the issue in depth but was relegated to a minor position in the program, we will restate the main findings here.

Exposure error in environmental epidemiology refers to less-than-perfect correlation (R_s) between surrogate (observed) exposure measures used in the statistical analyses and the actual doses to target organs that ultimately result in the health effects observed. Such errors may be due to sampling strategies, the instruments used, biases resulting from being indoors, or to non-linearities between inhalation and target organ doses, including respiratory defenses. Such errors may bias the observed slopes and intercepts (including perceived thresholds) and obscure the shapes of dose-response functions. When errors are normally distributed, slopes and intercepts are biased in proportion to R_s^2. Since it is rare to find even components of R_s exceeding 0.5, such biases may be large.

In addition, when two or more collinear agents have different degrees of exposure error, the variable with the least error will tend to dominate in a joint regression. This was the topic of our paper in the first Colloquium (Inhal Tox. 7:671-89). If one of these agents has severe measurement error (such as CO, for example), the true degree of its exposure collinearity will also be obscured in the ambient, so that it is not possible to exclude co-pollutants on the basis of low or moderate correlations among ambient measurements. We conclude that many authors have misinterpreted the findings of their regressions involving several pollutants; in the presence of differential exposure errors (which are to be expected), lack of significance of a co-pollutant should not be interpreted as lack of effect. All of this also applies to ambient temperature as an environmental agent (as opposed to a factor used for seasonal adjustments), since the true population exposure to heat or cold stress is not measured or even estimated.

Based on data supplied by the Gage Research Institute at the University of Toronto in which personal exposures to PM_5, SO_2, NO_2 and CO were measured simultaneously, we concluded that personal exposures tended to be less collinear than the corresponding ambient measurements, and that the relationships (R_s) between personal and ambient differed widely among pollutants, with PM the most disparate. This implies the likelihood that health responses that have been assigned to PM on the basis of ambient surrogates could actually be due to CO or NO_2 masquerading as PM through ambient collinearity.

We showed from published data that many of the properties ascribed to "coarse" particles ($CP=PM_{10}-PM_{2.5}$), including the perceived lack of correlation with $PM_{2.5}$ and poor performance as a predictor of health effects, may well be due to the extremely poor quality of the CP measurements. This calls into question any conclusions regarding the uniqueness of health responses to fine particles based solely on observational epidemiological studies.

The data on personal exposures to PM_{10} published by Lioy et al. (1990) show a great deal of variation in R_s, from about 0.15 to about 0.85. It is not possible to link R_s with the probability of health effects in such a meager data set, but we used a probabilistic simulation based on the distributions of personal and ambient exposures to show that biases of around 100 ug/m^3 in the perceived health effects thresholds are possible.

Because of the pervasiveness of exposure errors in environmental epidemiology, we believe that future authors should be required (by journal editors) to include a discussion of likely errors in the specific exposure measures used in their analyses, just as experimentalists are expected to provide evidence of the proper calibration of their instruments.

We must conclude that, with regard to the epidemiology of urban PM, neither the responsible agents nor the critical concentration levels have been identified with certainty.

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Ronald E. Wyzga, Electric Power Research Institute, Palo Alto, CA 94303
Frederick W. Lipfert, Environmental Consultant, Northport, NY 11768

One of the issues that surfaced during the final discussions of the Colloquium is the degree of coherence and unanimity in the various studies of acute mortality. A "consensus" position was espoused that pollutant collinearity was no longer an issue, for example. We disagree and addressed the importance of considering exposure error in a separate comment; because of differential exposure errors among co-pollutants, lack of significance in a joint regression should not be interpreted as showing lack of effect. Below we synthesize the evidence as portrayed by extant acute mortality studies, apart from exposure issues.

Three types of "meta" analyses are possible to address this issue. The earliest mortality studies purported to have identified a single agent (PM), and moreover, a nearly constant dose-response relationship in studies throughout the US and elsewhere. However, these studies often differed substantially in their analytical approaches and in the lags and copollutants considered in order to arrive at this appearance of conformity. These authors thus showed that when different methods are used in different cities (the first type of meta-analysis), it is possible to find some degree of uniformity (even though the physico-chemical nature of PM varied widely among the locations considered). Thurston et al. showed at this Colloquium that, when a common methodology is applied to 9 different cities (the second type), different results ensue, from no association to an association much stronger than has been seen heretofore. We reviewed the studies of daily mortality in Philadelphia and showed that similar disparities result when different methods are used in a single location (the third type). Further, we showed that the pollutant intercorrelations seen in Philadelphia are typical of other cities as well, implying that the findings of the various investigators in Philadelphia may also apply to other locations.

The degree of mortality "harvesting" present and the existence of truly chronic effects on mortality remain unanswered in all extant studies; it is tempting to compare the results of time-series with those of cross-sectional studies to examine these questions. However, it appears that long-term responses have been overstated by using coincident rather than the typically much higher cumulative exposure data; as shown in a poster paper at the Colloquium, there has been a steady downward trend in ambient levels of both TSP and $PM_{2.5}$. Acute responses may be understated because of exposure error; both types of studies may suffer from differential measurement errors in confounders. Further, there is no reason to pre-suppose that the physiological mechanisms and thus the causal agents would be the same for both acute and chronic responses. The existence of truly chronic mortality effects thus appears increasingly problematic, and the harvesting issue remains unresolved.

Much of the Colloquium was occupied with trying to identify the properties of PM that are responsible for its apparent associations with population health responses. To illustrate the difficulties of this task, we used data from the Philadelphia area including every-sixth-day measurements of PM_{10} from the city and a set of 6-day TSP and SO_4^{2-} data from up to 14 suburban stations ringing but not actually in the city. City PM_{10} was shown to be a good predictor of mortality, as expected. Our initial hypothesis was that suburban SO_4^{2-} could also predict city mortality because of the expected spatial uniformity of SO_4^{2-}, but that suburban TSP would be less successful. We found the opposite to be true, in spite of the expected lower exposure error for SO_4^{2-}. The relative superiority of non-sulfate particles in predicting health effects is also consistent with the findings of PM-health associations in (Western) areas with only minimal ambient SO_4^{2-} concentration levels.

VI. PRE-COLLOQUIUM WORKSHOP

Report of the Particulate Matter (PM) Research Strategies Workshop,

Park City, Utah, April 29-30, 1996

Morton Lippmann,[A] John D. Bachmann,[B] David V. Bates,[C]

Flemming R. Cassee,[D] Leendert van Bree,[D] Kevin E. Driscoll,[E] Robert F.

Phalen,[F] C. Arden Pope III,[G] Sidney C. Soderholm,[H] and William E. Wilson[B]

[A]New York University Medical Center, Tuxedo, NY

[B]U.S. Environmental Protection Agency, Research Triangle Park, NC

[C]University of British Columbia, Vancouver, BC, Canada

[D]National Institute of Public Health and the Environment, Bilthoven,

The Netherlands

[E]Proctor and Gamble Company, Cincinnati, OH

[F]University of California-Irvine, CA

[G]Brigham Young University, Provo, UT

[H]National Institute for Occupational Safety and Health, Morgantown, WV

Corresponding Author: Morton Lippmann, Ph.D., CIH
Nelson Institute of Environmental Medicine
New York University Medical Center
Tuxedo, NY 10987
Telephone: 914-351-2396
FAX: 914-351-5472

ABSTRACT

An informal 1-1/2 day workshop devoted to research needs on the health effects of airborne particulate matter (PM) was held in Park City, Utah on April 29 and 30, 1996, in conjunction with the Second Colloquium on Particulate Air Pollution and Health at Park City, Utah, on May 1-3, 1996. The objective of the Workshop was to prepare a holistic assessment of knowledge gaps and research opportunities for presentation at the penultimate session of the Colloquium. The Workshop reviewed the research progress made since the first PM Colloquium (Irvine, CA - January 1994) and the findings of recent major reviews of the PM literature by WHO-EURO, U.K. Health Department, RIVM in the Netherlands, and the U.S. EPA. It then discussed: 1) the nature of ambient PM; 2) population segments at special risk; 3) the nature of the health effects of concern; 4) the sources of ambient air PM; and 5) the implications of ambient air PM health effects on occupational exposure limits and occupational cohorts. The Workshop concluded that:

- A primary focus for further research should be on accumulation mode aerosol with the objective of disentangling the roles of its chemical constituents, as well as their interactive effects with each other and with coexisting gaseous criteria pollutants.

- Research is also urgently needed on the health effects of both the coarse mode PM_{10} and the ultrafine particles in the nuclei mode aerosol.

- There should be a continued focus on infants, the elderly, and people with pre-existing cardiopulmonary diseases.

- Further development and validation of animal models for human sensitive groups warrants high priority.

- Validated animal models are needed for target human populations in order to investigate: a) the roles of specific constituents of PM mixtures; b) the roles of exposure concentrations and durations on responses; c) some of the risk factors that predispose individuals to be responsive to PM exposures; d) physiological, biochemical, molecular and pathological correlates of mortality, tissue and organ damage, and chronic disease development.

Key Words:

community air
exposure
morbidity
mortality
national ambient air quality standard
particulate matter
research needs

INTRODUCTION

The membership of the Workshop, who are the authors of this paper, were selected on the basis of their backgrounds, expertise, and research experience to cover the range of current PM issues, i.e., exposure assessment, epidemiology, and controlled laboratory exposures. The focus of the Workshop was on determining the research needs related to the health effects of the complex mixtures of particles and vapors commonly encountered in the community air. As a starting point for identifying critical gaps and uncertainties, it was necessary to synthesize our collective knowledge of the nature, extent, and causes of health effects associated with general population exposures to such mixtures. A second objective was, to the extent possible, to describe the implications of our current knowledge of such health effects to PM exposures in occupational settings and to active and retired workers having chronic lung disease and/or elevated lung dust burdens as a result of their occupational exposures.

The summary of current knowledge, information gaps, and uncertainties expressed here reflects the collective views of the Workshop participants. We do not expect that these views, as expressed herein, will be considered as being "definitive", or representative of all perspectives on the available information on the health effects of PM, either alone or as part of an overall pollution complex. They are offered in order to provide input into the formulation a research agenda for PM that will be initiated as part of the completion of the current, court-mandated review of the adequacy of the current PM National Ambient Air Quality Standard (NAAQS) that is scheduled for completion in 1997.

OUTLINE OF WORKSHOP EFFORT

Prior to the Workshop meeting, each member prepared a background document on a particular topic area, covering: a) the current state of common knowledge; b) conventional wisdom that warrants reconsideration; and c) critical knowledge gaps that are amenable to resolution through ongoing or new research endeavors. These individual efforts, as modified by the Workshop discussions, are being submitted for publication in the Colloquium Proceedings.[1] The background documents were circulated to all Workshop members in advance. At the Workshop, the author of each background document led an open discussion on his topic and findings. Summaries of the research recommendations made by Workshop participants are provided at the end of this paper.

In preparation for the presentation of a summary report of the Workshop at the Colloquium and for this paper, we organized our discussions as follows:

A. Progress since PM Colloquium I at Irvine, CA in January 1994. [Papers from Colloquium I were published in Inhalation Toxicology[2] and as full Proceedings].[3]

B. Findings of major reports on PM effects on human health by authoritative

entities.

C. Framework for Workshop discussions.

D. Identification of urgent research needs.

A. PROGRESS SINCE PM COLLOQUIUM I AT IRVINE, CA IN JANUARY 1994

We view the progress made over the last 27 months in our collective understanding of the effects of ambient air PM on human health as being remarkable in volume and content for such a relatively short interval. While the remaining unresolved issues remain quite large and formidable, we are at least at the stage of being better able to formulate the critical research questions. Furthermore, there are clearly many highly competent research teams prepared to address them effectively. It is essential that coordinated efforts be made by interested parties to ensure that adequate resources and suitable funding mechanisms will be available to facilitate the necessary research.

We summarized the considerable progress made since the Irvine Colloquium in terms of:

1. Time-Series Studies of Acute Mortality and Hospital Admissions
2. Cross-Sectional Studies of Annual Mortality
3. Identification of PM Components of Concern
4. Identification of Thresholds
5. Extent of Human Exposure to PM of Outdoor Origin

1. Time-Series Studies

In their summary of the mortality time-series studies at the Irvine Colloquium, Pope et al.[4] cited 10 peer-reviewed studies from communities around the world. Five of these studies were based on measurements of PM concentrations of particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), and 5 used approximations to convert total suspended particulate matter (TSP) or coefficient of haze (CoH) to PM_{10} equivalents. They noted the consistency of the small, but generally statistically significant relative risks. Much of the open discussions at Irvine centered on the biological plausibility of the associations, and whether the associations could have been due to the nature of the assumptions made in specifying the statistical models used, or in accounting for the influence of weather on mortality. Furthermore, there was concern that most of the studies did not consider the possible influence of other pollutants in the complex ambient air mixture.

The recently released USEPA PM Criteria Document (CD)[5] cited peerreviewed mortality studies using measured PM_{10} concentrations from 8 additional communities, including many that explicitly examined the influence of model specifications, use of various approaches to account for the influence of weather variables, and of multiple pollutants. It also cited acute-mortality

time-series results reported by Schwartz et al.[6] from the Harvard 6-city study in relation to measured concentrations of fine particles, i.e., particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$).

Both the Schwartz et al.[6] paper, and the paper presented at the Park City Colloquium by Dockery et al.[7] for a time-series analysis of daily mortality in Philadelphia during 1992 and 1993, showed that daily mortality was more closely associated with $PM_{2.5}$ than with PM_{10}. The only exception was for Steubenville, one of the Harvard six-cities, where the PM_{10} and $PM_{2.5}$ were highly intercorrelated.

At the Irvine Colloquium, Pope et al.[4] cited four time-series studies of hospital admissions for respiratory diseases. By contrast, the latest PM CD cited thirteen such studies. The CD also cited two studies[8,9] that provided the first reports of significant associations between ambient PM concentrations and hospital admissions for cardiovascular disease (CVD), which supplements prior reports about total and respiratory hospital admissions. (A third report on a CVD association with PM was presented at the Park City Colloquium by Fennelly and Bartelson.)[10]

Based upon this greatly expanded body of time-series data, we find:

A. Prior concerns that observed PM-health associations are due largely to confounding by weather and/or to inappropriate model specification have been largely overcome. This has been done primarily through the development of reasonably well specified and rigorous modeling approaches and the reanalysis of various data sets using alternative approaches.

B. Prior concerns about confounding by pollutant gases have been reduced.

C. The evidence for coherence[11] among mortality and hospital admissions has been strengthened.

D. The evidence for treating fine-mode particles, as indexed by $PM_{2.5}$, and coarse mode particles, as indicated by PM_{10}-$PM_{2.5}$, as separate pollutants, has been strengthened.

2. Cross-Sectional Studies of Annual Mortality

Since the Irvine Colloquium, the first longitudinal cohort study of the influence of long-term PM exposure on annual mortality by Dockery et al.,[12] has been supplemented by the American Cancer Society Study of over a half million people in 151 communities.[13] On the basis of the consistency of the findings between these two studies that considered a wide-range of individual risk factors, and with those from earlier ecological studies of annual mortality,[14] we find that:

A. Smoking and other individual risk factors do not account for the significant associations between ambient air PM and annual mortality rates.

B. The strongest associations are with fine particle concentration ($PM_{2.5}$) and with

the sulfate ($SO_4=$) content of $PM_{2.5}$ rather than indicators of the mass concentrations of coarser particles (TSP or PM_{10}).

C. The cumulative annual mortality associated with PM exposures is greater than that from excess daily mortality during peak exposures, suggesting significant life-span shortening.

3. Identification of PM Components of Concern

Our continuing inability to identify specific PM constituents that may account for disproportionate portions of the health effects associated with PM exposures limits our ability to understand the nature of the underlying exposure-response relationships. It also impedes the initiation of efficient control strategies.

The increasing concern about fine particles evident since the Irvine Colloquium has stimulated greater interest in some specific chemical components of the accumulation mode aerosol, as well as of the more transient ultrafine particles in the nuclei mode. The ultrafine particles contribute little mass to the fine fraction. However, they dominate the particle surface area and the particle number concentration. The potential importance of particles with diameters of ~ 20 nm is illustrated by the evidence for adverse effects from studies by Oberdorster et al.[15] with very low mass concentrations of insoluble ultrafine particles and by Chen et al.[16] with very low H+ concentrations on ultrafine particle surfaces. We need to know more about how insoluble ultrafine particles rapidly penetrate the respiratory epithelium and how acidic ultrafine particles stimulate mediator releases from respiratory epithelial cells.

From among the numerous chemical constituents of the accumulation mode PM, our discussions focussed on the strong acid component of the aerosol (H+), $SO_4=$, the transition metals that stimulate reactive oxygen species (i.e., Fe, V, Ni, Cu, Zn), organics, and allergens, as well as on potential synergistic interactions among these constituents.

H+ remains a viable candidate for a disproportionate share of the effects produced in populations by the fine particles on the basis that: 1) it is the only constituent that has produced physiological and toxicological responses in controlled short-term exposure studies at near ambient concentrations that are consistent with effects seen in population studies; and 2) it has been found to be the single PM index most closely associated with excess hospital admissions for respiratory diseases in Toronto[17] and with respiratory and CVD mortality and hospital admissions in Buffalo, NY.[18] On the other hand, in several other epidemiologic studies in which H+ was measured, it has not been measured at generally detectable levels, or found to be as highly correlated with the responses as fine particle mass or sulfate.[6,19]

$SO_4=$ has been as closely, or often more closely associated with human mortality and morbidity indices than other PM metrics.[20] This could be due to its relatively small measurement error, its utility as a conservative metric of exposure to PM of outdoor origin both indoors and outdoors, its close association with H+, or its being closely associated with other reactive chemical species in the atmosphere. For example, at the Park City Colloquium, Friedlander and

Yeh[21] demonstrated that $SO_4=$ was closely associated with peroxides in ambient air, and that peroxides were plausible candidates for causal chemical species in relation to human health effects.

Transition metals in soluble forms are released to the atmosphere from combustion sources as ultrafine particles, and can build up in the atmosphere on accumulation mode particles. Recent research presented at the Park City Colloquium by Ghio et al.[22] and Dreher et al.[23] have demonstrated that these metal ions, when administered via intratracheal instillation, can generate reactive oxygen species in the lungs that could account for many of the adverse cardiopulmonary health effects of concern. However, there have not yet been any reports demonstrating that such effects can be produced via inhalation at PM concentrations near those measured in the ambient air. On the other hand, long-term exposure to low concentrations of carcinogenic trace metals could be related to the suggestive evidence from the chronic mortality epidemiology for PM-associated-elevations in cancer risk reported by Dockery et al.[12]

Trace organics in PM could also play a role in the suggestion of excess cancer risks associated with long-term PM exposure. Also, to the extent that organics within thoracic PM stimulate the generation of reactive oxygen species, they may possibly also play a role in the cardiopulmonary effects associated with PM exposures.

Airborne allergens are a well-established class of causal agents for cardiopulmonary health effects, with strong seasonal influences. However, most of the aeroallergens found outdoors are of natural origin, and are not amenable to control by regulatory agencies. Airborne allergens of indoor origin, such as those from dust mites, animal dander, roaches, molds, mildew, and fungi, can also be important confounding cardiopulmonary stressors not amenable to control by governmental agencies. In any case, research is needed in order to better determine the interactive effects of exposures to abiotic anthropogenic air pollutants and aeroallergens.

There is an urgent need for studies of the effects of the kinds of complex mixtures typically present in regional and urban airsheds. The papers presented at the Park City Colloquium by Godleski, et al.[24] on excess mortality in hypertensive and bronchitic rats exposed to concentrated Boston winter accumulation mode aerosol, and by Kleinman et al.[25] on enhanced cellular and physiological effects in aged rats exposed to laboratory-generated mixtures of mineral dust, acidic aerosol, and ozone provide strong evidence that laboratory studies of "realistic" complex PM-gas mixtures can produce biological effects comparable to those reported in human populations at much lower concentrations than those required for the gaseous pollutants within the mixtures. As these types of studies more clearly establish the nature and extent of the effects that can be produced by complex PM-gas mixtures, it may be possible to disentangle the roles of one or more of the specific components within the mixture by selective removal or neutralization of components and/or by selective enhancement of the concentration ratios of some of the more potent components.

In summary, we now appear to on the threshold for rapid expansion of our knowledge of underlying biological mechanisms that can account for the kinds of cardiopulmonary effects

associated with population exposures to PM in ambient air. We now have more testable hypotheses as well as new technologies for generating more relevant test atmospheres for controlled exposure studies. These advances, when combined with the recently developed tools of molecular biology, analytic biochemistry, pathological analyses, and functional assessment provide the sensitive means needed for effective testing of our more sophistical hypotheses.

4. Evidence for Thresholds

The search for evidence of effective thresholds in large population studies of air pollution health effects continues. There are inherent limitations associated with measurement errors in both the exposure and the effects estimates. There are also limitations imposed by a broad range of sensitivities associated with constitutional factors and other environmental and disease factors that vary across human populations. The Park City Colloquium paper by Cifuentes and Lave[26] was interpreted to suggest different effective thresholds in Philadelphia and Santiago, Chile, but not in Birmingham, AL. Various other authors have explored for thresholds using quintile or quartile analysis of PM levels or by estimating the exposureresponse relationship with non-parametric smooths of PM, controlling for other factors. Such approaches have been used for many areas (including Philadelphia). Overall there is not yet consistent evidence available for a threshold, and the majority of the studies suggest a monotonic, near-linear, exposure response relationship.

5. Exposure to PM of Outdoor Origin

There has been important progress since the Irvine Colloquium in our understanding of the relationships between central station pollutant concentrations data and population distributions of exposures.

It has long been known that the fine mode and coarse mode components of the ambient aerosol have distinctly different sources and chemical compositions, and that reductions in human exposures to fine particles will necessitate quite different kinds of emission controls than those developed for and traditionally applied for coarse particle control. What is new in recent years is a body of data on the extent of penetration of PM of outdoor origin into indoor environments and their persistence indoors after their penetration. All thoracic particles (PM_{10}) of outdoor origin can infiltrate indoors with high efficiency. The non-reactive fine particles persist in the indoor air for many hours. Reactive fine particle components, such as H+, once indoors, are gradually neutralized by ammonia from indoor sources. The coarse component of PM_{10} decays rapidly, once indoors, by sedimentation. Reactive pollutant vapors, such as ozone (O_3) and sulfur dioxide (SO_2) rapidly decay by reactions with interior surfaces.

Indoor fine particle mass concentrations are generally poor surrogates for exposures to fine particles of outdoor origin because of the influence of fine particles of indoor origin (e.g., from smoking or cooking). On the other hand, $SO_4=$, being present as non-reactive fine particles, formed in the atmosphere on a regional scale, can serve as an excellent tracer for fine particulate matter of outdoor origin.[5,20]

By contrast, the mass concentration of PM_{10} with widely varying ratios of coarse to fine mass in terms of region, local area, and time, is highly dependent on the presence of local sources of coarse particles and wind patterns. As a result, there can be much greater variations from one monitoring site within a community to another in PM_{10} mass concentration than in fine particle mass concentration. Thus, if PM_{10} monitoring data are to be used for epidemiological studies, then multiple monitoring site averages will provide much more reliable estimates of population exposure to PM_{10} than any single site's data, except in situations where an extended set of local calibration studies have demonstrated that a single site can provide a good representation for the larger community. For coarse PM, indoor sources, such as dust resuspension from furniture and floors, can dominate personal PM_{10} exposures.

It has also become clear in recent years that there are important unresolved technical issues in the measurement of the mass concentrations of ambient air PM_{10}. We have learned that the semivolatile components, especially ammonium nitrate, but also woodsmoke and some organic components of photochemical smog, are not fully retained on sampling filters. In the western U.S., where nitrates and organics can constitute large fractions of PM_{10} network monitoring data can significantly underestimate actual PM_{10} exposures.[27] The problem is even more severe for fine fraction of PM_{10} since essentially all of the semivolatile PM_{10} is contained within the fine fraction. Also, the problem may be more severe for PM monitors with heated inlets than for manual samplers.

In the eastern U.S., where there are much lower concentrations of ammonium nitrate and much larger concentrations of acidic sulfates, there can be another, quite different systematic error in reported PM_{10} concentrations. This is because the acidic sulfates are strongly hygroscopic and take up water vapor when ambient humidities are elevated, as is typical during the summer in the humid eastern U.S. Some of the retained water remains on the filter, even after equilibration to standard conditions in the analytic laboratory. As documented in the latest USEPA PM Criteria Document,[5] a large fraction of the reported PM_{10} mass in the eastern U.S. cannot be accounted for by chemical analyses of sampling filters and presumably is particle-bound water. Under such conditions, reported PM_{10} concentrations in the east overestimate true ambient PM exposures. Since almost all of the sulfate is in the fine fraction, this problem is also more severe for the fine fraction than for PM_{10} as a whole.

The selection of an optimal cut-size for the aerodynamic separation of the fine and coarse fractions of PM_{10} is complicated by the different humidity ranges in the east and west, as well as by the different proportions of fine and coarse particles. In the arid west essentially all of the fine mode particles are below 1 μm in diameter, and strong winds can produce a coarse mode distribution tail with a significant mass in the 1 to 2.5 μm range. Thus, a 1 μm cut-size might be ideal for arid areas of the western U.S. By contrast, in the humid eastern U.S., a significant portion of the hygroscopic sulfate aerosol can be found in the size interval between 1 and 2.5 μm, and coarse mode intrusion into this size interval is generally low. Thus, for the eastern U.S., an aerodynamic cut-size at 2.5 μm diameter is preferable.

Since it is unreasonable to expect that future PM standards will accommodate regional variations

in cut-size, accommodations to differing regional conditions could be considered. One relates to the sharpness of the cut. Some of the available fine particle data and epidemiological studies relied on the virtual dichotomous sampler, which has a nominal cut-size of 2.5 μm and a geometric standard deviation (σg) of ~ 1.2. Most of the rest of the available data was generated by the Harvard, NYU and Health Canada research groups using an impactor with a sharp cut at 2.1 μm ($\sigma g \leq 1.1$). Whatever cut-size is used, it is clearly preferable to have the sharpest practical cut characteristic ($\sigma g \leq 1.1$) to minimize the intrusion of coarse mode particles into the fine mode fraction.

A second means of accommodation was described at the Park City Colloquium by Lundgren et al.[28] They described an analytical method that used data on the mass and trace element composition of the fine and coarse fractions to calculate the true accumulation mode concentration.

B. MAJOR REPORTS ON PM EFFECTS ON HUMAN HEALTH

In the interval between the Irvine and Park City Colloquia, four authoritative entities have drawn conclusions about the health impacts of ambient air PM.

The World Health Organization - European Region (WHO-EURO) has prepared revised Air Quality Guidelines for a variety of air pollutants, including PM. It's earlier Guidelines[29] were based on the premise that there were no observable adverse effects evels (NOAELS) and that public health could be protected by establishing a lower concentration limit than the NOAEL using a safety factor. The latest WHO-EURO expert committee for PM concluded that there was no current basis for establishing a NOAEL for PM.[30] It recommended instead that the exposure-response relationships for PM_{10} and $PM_{2.5}$, as interpreted and tabulated by the expert panel, be reported with tabular guidance and interpretive text for use by national authorities in establishing their own air quality standards. Thus, the burden is on the national authorities to determine their own acceptance limits for the public health impacts of exposures to ambient PM.

A second authoritative report, from the U.K. Department of Health concluded that, with typical British understatement, "In terms of protecting public health it would be imprudent not to regard the demonstrated associations between daily concentrations of particles and acute effects on health as causal."[31]

A third report, the 1993 Revision of the PM Criteria Document issued by the National Institute of Public Health (RIVM) in the Netherlands, concluded that there was:

- "Coherent and consistent" results from epi-studies, especially for associations with mortality
- No apparent threshold
- Some preliminary quantitative health risk estimates for various PM_{10} levels (24 h)

Finally, the most thorough and comprehensive report now available is the new USEPA PM

Criteria Document.[5] Among its numerous conclusions are:

- The chemical and physical differences between fine-mode and coarsemode particles have important implications for evaluation of the health and welfare effects of such particles as distinct pollutant subclasses.

- Our current understanding of the toxicology of ambient particulate matter suggests that fine and coarse particles may have different biological effects.

- The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, misspecification of concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure other than PM, weather, or other variables, nor confounding of PM effects with effects of other factors.

- Within the overall PM complex, the indices that have been most consistently associated with health endpoints are fine particles, thoracic particles (PM_{10} or PM_{15}), and sulfate ($SO_4=$). Less consistent relationships have been observed for TSP, strong acidity ($H+$), and coarse PM (PM_{10}-$PM_{2.5}$)

- There is evidence that older adults with cardiopulmonary disease are more likely to be impacted by PM-related health effects (including mortality) than are healthy young adults. The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among this elderly population is bolstered by: 1) the more uniform distribution of fine particles across urban areas and their well-correlated variation from site to site within a given city; 2) the penetration of ambient particles to indoor environments (where many chronically ill elderly individuals can be expected to spend most of their time); and 3) the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles.

C. FRAMEWORK FOR WORKSHOP DISCUSSIONS

Upon completion of our reviews and discussions of the background documents prepared by each member of the Workshop panel, we continued our discussions along broader, more integrated themes. There were:

1. The nature of ambient PM as it relates to human health effects.
2. Population segments at special risk.
3. The nature of the effects of concern.
4. The sources of PM with special reference to control strategies.
5. The implications of current knowledge of the health effects of ambient PM of outdoor origin on occupational exposure limits and occupational cohorts.

With regard to the nature of ambient PM in relation to human health effects, we concluded that:

- A primary focus for further research should be on accumulation mode aerosol with the objective of disentangling the roles of its chemical constituents, as well as their interactive effects with each other and with coexisting gaseous criteria pollutants.

The focus is warranted because the best established PM-associated human health effects are most closely associated with the concentrations of fine particle mass, sulfate, and hydrogen ion. Other accumulation mode constituents warranting further investigation are the transition metals and organics on the basis of their demonstrated biological effects in laboratory assays and their potential carcinogenic effects.

- Research is also urgently needed on the health effects of both the coarse mode PM_{10} and the ultrafine particles in the nuclei mode aerosol.

While epidemiological evidence for coarse mode PM_{10} (i.e., $PM_{10}PM_{2.5}$) is, at best, only suggestive, it is likely that at least some of the effects associated with PM_{10}, such as excess bronchitis incidence and exacerbation of asthma were due more to coarse mode PM_{10} than to the $PM_{2.5}$ fraction. It is well known that occupational exposures to mineral dusts causes "industrial bronchitis", and that dust and fog exposures can exacerbate asthma.

Heyder et al.,[32] at the Park City Colloquium, provided a report of the first study linking human responses to PM more closely to the number concentration than to the mass concentration of fine particles. This, plus the more speculative evidence from animal inhalation studies with high number concentrations (but low mass concentration) of insoluble ultrafine particles[15] and of acidic ultrafine particles,[16] demonstrates the need for more intensive epidemiological and controlled exposure studies of the health effects of ultrafine aerosols.

As for the populations of special concern with regard to the human health effects of exposures to PM of outdoor origin, we concluded that:

- Continued focus on infants, the elderly, and people with pre-existing cardiovascular and pulmonary diseases is warranted in further epidemiological studies, especially in studies relating quantitative determinations of individual exposures in relation to morbidity endpoints.

Further development and validation of animal models for human sensitive groups warrants high priority.

The availability of validated animal models for at least some, if not all, of the human populations likely to be most susceptible to health effects associated with ambient air PM exposures will make it possible to investigate a number of important factors, such as: a) the roles of specific constituents of PM mixtures; b) the roles of exposure concentrations and durations on responses; c) some of the risk factors that predispose individuals to be responsive to PM exposures; d)

physiological, biochemical, molecular and pathological correlates of mortality, tissue and organ damage, and chronic disease development.

With regard to effects of concern, emphasis should continue to focus on effects reported in the epidemiological studies and their correlation in animal models of susceptible populations. These effects include:

- sudden death
- reduced longevity
- admission to emergency room and hospital
- lost time (from school or work)
- supplemental medication usage
- increased rate of infections
- increased symptom rates
- reduced lung function

With regard to PM sources and their implications for control strategies, we note that the prior NAAQS, based on TSP, and the current NAAQS, based on PM_{10} being mass concentration limits, drive control strategies toward an emphasis on limiting emissions of primary particles. Since primary particles are largely coarse particles, there has been relatively less attention paid to controlling gas phase precursers of fine particles. Also, state and local control agencies recognize that emission controls on gaseous precursers of fine particles will have little impact on $PM_{2.5}$ concentrations within their own jurisdiction and cannot influence the ambient $PM_{2.5}$ concentrations attributable to source emissions in upwind regions.

It follows that future control programs for $PM_{2.5}$ can only be fully effective if they are based on regional rather than local control strategies.

With regard to the implications of our increased understanding of the health effects of ambient air PM of outdoor origin on workers with chronic exposures to dusts and vapors, our primary concern focussed on the prospects that such workers are likely to constitute a susceptible subpopulation. It is well established that long-term exposure to mineral dusts can lead to chronic bronchitis and accelerated loss of lung function, and that these conditions can progress even after the occupational exposures end. Miners and other workers in dusty trades may retire with lung function in the normal or near normal range and then become progressively disabled. This is because of dust that accumulates around small airways, and the loss of lung recoil, which is a normal part of lung aging, results in airflow obstruction. They would become a sensitive population group in terms of pneumonia or if cardiovascular disease is added to an existing burden. Registries of such workers, if enrolled in prospective cohort studies, may be ideal populations for further studies of both acute and chronic air pollution mortality and morbidity.

In designing future studies of the health effects of occupational exposures to PM or to mixtures of PM and irritant vapors, consideration should be given to the hypotheses generated by the recent epidemiological research on ambient air PM. Attention should be paid to cardiovascular

and respiratory symptoms and functions, in occupationally exposed workers, as well as to daily variations in their responses that may be related to variations in their exposures to environmental pollutants.

D. URGENT RESEARCH NEEDS

For the purpose of this paper, our research recommendations are summarized in terms of:

1. Particle Composition and Size
2. Studies of Human Populations
3. Animal Models for Toxicological Studies
4. Exposure Assessment

1. Particle Composition and Size

There is a critical need to identify the components and size characteristics of ambient PM that contribute to the adverse responses demonstrated in epidemiology studies. Understanding which components or interactions between components are essential to the toxicity of PM will be useful in designing appropriate monitoring and potential control strategies. A more detailed discussion of data gaps and research needs in this area was presented at the Park City Colloquium by Driscoll and Jarabek.[33] Some urgent research areas include:

- Definition of interactions between PM components. Most studies have focused on exposures to only one or two components of ambient PM. There is increasing evidence that interactions occur between components of ambient PM as well between PM and gaseous pollutants, and that such interactions result in increased toxicity. Better definition of interactions between PM components is needed, as are studies on whole (concentrated) ambient PM. Since chemical reactions between materials on the surfaces of particles may account for the synergistic effects of PM components, a better understanding of this chemistry, as it relates to the formation of more toxic materials as well as the interactions between particle surfaces and host factors (cells, proteins, lipids) within the lung, is needed.

- Identification of critical targets of PM effects. Cytotoxicity, inflammation, oxidant stress and altered lung cell function have all been reported as aspects of the respiratory tract response to relatively high concentrations of ambient PM components. Defining the critical in vivo targets (e.g., epithelial cells, macrophages, upper or lower airways, etc.) and the nature of the effects (e.g., oxidant production, cytokine release) within and outside the respiratory tract will be key to developing more sensitive approaches and biomarkers to assess the adverse effects of PM in toxicology and clinical studies.

- Toxicity of ultrafine particles. Studies on ultrafine particles indicate that they can be highly toxic in the lung, particularly when exposure is to large numbers of singlet particles. Studies are needed to further define environmental exposure to ultrafine particles as well as the nature of these particles to better appreciate the relevance of recent laboratory findings.

Additionally, a better understanding of the mechanisms underlying the toxicity of ultrafine particles is needed.

- Dosimetry. In considering exposure-response relationships for particles, at present, it is not clear which dose metric (e.g., mass, surface area, particle number) is most appropriate for assessing fine particle exposure as it relates to potential toxicity. Additional studies characterizing relationships between particle surface, number and mass and responses to exposures to ambient PM and its components are needed.

- Interactions. The fine particle component of ambient particulate matter provides a large surface area onto which materials may become adsorbed (vapors, gases) and react resulting in the formation of toxic materials such as reactive oxygen species. Additionally, fine particles may act as vehicles to deliver surface adsorbed materials to sites in the lung they would not otherwise reach in significant concentration. The extent to which fine particles act to promote reactions between components of ambient pollution and deliver the products to the deep lung needs to be investigated. This information could provide insights in to potential mechanism of toxicity, as well as guide development of better approaches for generating test aerosols that most closely mimic ambient PM.

2. Studies of Human Populations

Current epidemiologic evidence suggests that thoracic particulate air pollution, at levels common to many urban and industrial areas in the United States, contributes to human morbidity and mortality. Long-term, repeated exposure increases the risk of chronic respiratory disease and the risk of cardiorespiratory mortality. Short-term exposures can exacerbate existing cardiovascular and pulmonary disease and increase the number of persons in a population who become symptomatic, require medical attention, or die. The pattern of cardiopulmonary health effects associated with particulate air pollution that has been observed by epidemiological studies is currently the strongest evidence of the health effects of this class of pollutants. Nevertheless, the epidemiological studies have important limitations that stem largely from the use of people who are living in uncontrolled environments, and who are exposed to complex mixtures of particulate air pollution.

In addition to providing limited information about biological mechanisms, current epidemiological studies provide relatively meager information regarding linkages between ambient and personal exposures, and are unable to fully explore the relative health impacts of various constituents of air pollution. Future research needs to integrate epidemiological studies and exposure assessment studies. Efforts to understand relationships among different ambient air pollutants, as monitored at central monitoring sites, and their relationships to personal exposures need to be considered in studies of associations of exposures with cardiorespiratory health endpoints. Such an approach can be used with cohort- (or panel-) based time-series or crosssectional studies. Ideally, structurally linked multi-area studies would be used to help disentangle independent effects or potential interactions among risk factors that exist and are highly correlated in some areas but not in others.

Future research needs to help provide a better understanding of the relative importance of chronic and acute exposures. Much of the recent epidemiological effort has focused on effects of acute exposure, primarily because of the relative availability of relevant time-series data sets. However, the effects of chronic exposure may be more important in terms of overall public health relevance. Such research is also needed to provide a better understanding of susceptible populations. For example, individuals susceptible to serious effects of acute exposure may only be those with existing respiratory and/or cardiovascular disease; but, a much larger segment of the population may eventually be seriously affected by chronic, long-term exposure.

3. Animal Models for Toxicological Studies

The paucity of toxicity data on ambient particulate matter is due to the lack of validated and relevant laboratory animal models having the characteristics of compromised human subjects. The validation of such animal models will be very useful and illuminating in explaining the epidemiological findings. Animal models that have been developed for human pulmonary and cardiovascular diseases include respiratory allergy (asthma), chronic bronchitis, pulmonary emphysema, aging, pulmonary hypertension, congestive heart failure and respiratory infection. Such models were described in detail at the Park City Colloquium by Cassee and Van Bree,(34) but it will be necessary to further develop and validate these models. Important questions with respect to such models are: 1) how do they reflect the pathological features of human diseases, and what parameters should be used to measure these effects?; 2) can we control the severity of the disease?; and 3) what do we know about the altered dosimetry in compromised animals and what is the stability and the reproducibility of a model? Moreover, most of the available models can only be used for acute and subacute toxicity studies, but there is a urgent need for models that can be used in chronic or subchronic toxicity studies. Some of these questions can only be properly addressed when we know more about which human populations are experiencing the various kinds of effects and what kinds of exposures are associated with these effects.

4. Exposure Assessment

Improvements are needed in all of the PM measurement methods, especially in terms of methods that provide continuous analyses of ambient concentrations and/or integral analyses over extended time intervals. Such methods can provide better data for both exposure and compliance analyses and may also, at the same time, reduce monitoring costs in relation to daily manual sampling and analyses of PM filters. These needs were described in detail at the Park City Colloquium by Wilson.[35]

The data generated by these improved measurement methods can also be used for systematic studies of exposure misclassification and measurement error. Such studies can provide an improved basis for the analysis of population distributions of exposures in epidemiological studies, and for analyses of population distributions of exceedances of ambient air quality standards for risk analyses.

Other important exposure related PM research needs include:

- Accumulation of more comprehensive information on the particle size distribution of ambient PM in representative cities in different parts of the U.S. having different source types. A comparison of particle size distributions by count and mass is especially important.

- Determinations of which species and size of PM components are sufficiently evenly distributed across large urban areas to be suitable for epidemiological studies.

- Development of appropriate exposure assessment protocols need to be developed for epidemiological studies that test specific hypotheses.

- Enhancement of the database on infiltration ratios (ambient into microenvironments) and activity patterns (time in various microenvironments) is needed to improve exposure assessments for epidemiological studies.

- Development of improved methods for measuring the concentrations of biological particles including endotoxins, pollens, spores, and insect debris in morbidity studies.

- Characterization of size, composition and concentration of concentrated ambient particles in laboratory exposure studies, including measurements of co-existing gaseous pollutants and toxic gases dissolved in particle-bound water.

- Development of better understandings of ambient/indoor/personal exposure relationships, their significance for various epidemiological studies, and how they can be used to improve assessment of exposure to ambient PM.

In addition, better integration/coordination of compliance and epidemiological monitoring is needed. Finally, in developing a Federal Reference Method (FRM), it is important to specify precise methods suitable for determination of trends and of compliance with PM mass standards without limiting improvements in measurement technology for continuous or long-term monitors or for techniques that measure all components of PM mass.

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VII. PARTICIPANTS

Abbey, David E.
Loma Linda University, U.S.A.

Ackermann-Liebrich, Ursula
University of Basle, Switzerland

Allen, George A.
Harvard University, U.S.A.

Amendola, Francis A.
Kennecott Corporation, U.S.A.

Anderson, Elizabeth L.
Sciences International, Inc., U.S.A.

Andress, Kris
Brigham Young University, U.S.A.

Andrews, Larry
Los Alamos National Laboratory, U.S.A.

Asgharian, Bahman
CIIT, U.S.A.

Aust, Ann E.
Utah State University, U.S.A.

Avol, Edward L.
USC School of Medicine, U.S.A.

Bachmann, John
EPA, U.S.A

Bahadori, Tina
Harvard University, U.S.A.

Baldwin, Bryan
Southern Company Services, U.S.A.

Ball, James C.
Ford Motor Co., U.S.A.

Barber, Allen P.
BHP Minerals, U.S.A.

Bates, David V.
University of British Columbia, Canada

Becker, Susanne
EPA, NHEERL, U.S.A.

Bennett, William D.
University of North Carolina, U.S.A.

Black, Karlyn G.
California Air Resources Board, U.S.A.

Blase, Kurt
Kilpatrick & Cody, U.S.A.

Boucher, Kenneth M.
University of Utah, U.S.A.

Bowles, Jeff
University of Utah, U.S.A.

Brauer, Michael
University of British Columbia, Canada
U.S.A.

Bucher-Bartelson, Becki L.
National Jewish Center for Immunology,

Caldwell, Jane
EPA, U.S.A.

Cass, Glen R.
Calif. Institute of Technology, U.S.A.

Cassee, Flemming R.
National Institute of Public Health,
The Netherlands

Chen, Lung Chi
New York Univ. Med. Ctr., U.S.A.

Chick, Nancy D.
CO Dept. of Public Health, U.S.A.

Cholakis, James M.
JMC Associates, U.S.A.

Chow, Judith C.
Desert Research Institute, U.S.A.

Cifuentes, Luis
P. Universidad Catolica de Chile, Chile

Clayton, Richard D.
Geneva Steel, U.S.A.

Coburn, Timothy C.
Natl. Renewable Energy Lab, U.S.A.

Cohen, Aaron J.
Health Effects Institute, U.S.A.

Cohen, Beverly S.
NYU School of Medicine, U.S.A.

Connery, Robert T.
Holland and Hart, U.S.A.

Cooper, John A.
TRC Environmental, U.S.A.

Costantini, Maria G.
Health Effects Institute, U.S.A.

Crapo, Matt
IML Air Science, U.S.A.

Cui, Wenxuan
Brigham Young University, U.S.A.

Daisey, Joan
Lawrence Berkeley Lab, U.S.A.

Dalley, Bob
Division of Air Quality, Utah, U.S.A.

Dasgupta, Purnendu K.
Texas Tech University, U.S.A.

Devlin, Robert B.
EPA, U.S.A.

Ding, Yiming
Brigham Young University, U.S.A.

Divine, Barbara J.
Texaco, Inc., U.S.A.

Dockery, Douglas
Harvard Sch. of Public Health, U.S.A.

Dreher, Kevin L.
EPA, U.S.A.

Driscoll, Kevin
Protor and Gamble, U.S.A.

Du, Alicia
Brigham Young University, U.S.A.

Eatough, Delbert J.
Brigham Young University, U.S.A.

Fairley, David
Bay Area AQMD, U.S.A.

Fennelly, Kevin
Natl. Jewish Ctr. for Immunol., U.S.A.

Fletcher, Brent R.
BHP Copper Company, U.S.A.

Freeman, A. Myrick III
Bowdoin College, U.S.A.

French, Timothy A.
Neal Gerber & Eisenberg, U.S.A.

Friedlander, Sheldon
UCLA, U.S.A.

Gerritson, Stephen L.
Lake Michigan Air Directors Consortium, U.S.A.

Ghio, Andrew
EPA, U.S.A.

Godleski, John
Harvard School of Public Health, U.S.A.

Gordon, Terry
NYU Medical Center, U.S.A.

Greenbaum, Daniel S.
Health Effects Institute, U.S.A.

Groten, Eric A.
Brown McCarroll & Oaks Hartline, U.S.A.

Guidotti, Tee
University of Alberta, Canada

Hart, Georgia
Schuller International, Inc., U.S.A.

Hauck, Helger R.
Inst. for Environ. Hygiene, Austria

Henderson, Alan J.
Texas Natural Res. Conserv. Comm., U.S.A.

Hering, Susanne V.
Aerosol Dynamics, Inc., U.S.A.

Hesterberg, Thomas W.
Schuller International Inc., U.S.A.

Hirsh, Alan R.
Smell & Taste Treatment/Research Foundation, U.S.A.

Hoek, Gerard
Harvard Sch. of Public Health, U.S.A.

Hofmann, Werner
University of Salzburg, Austria

Hoke, Steve H.
USACHPPM, U.S.A.

Hysenaj, Sheelagh K.
Environment Canada, Canada

Ito, Kazuhiko
NYU Med. Ctr., U.S.A.

James, Anthony C.
ACJ & Associates, U.S.A.

Janssen, Nicole
University of Wageningen, The Netherlands

Jarabeck, Annie
EPA, U.S.A.

Jennison, Brian L.
Washoe Co. Dist. Health Dept., U.S.A.

Katz, Stacey A.
EPA, U.S.A.

Keady, Pat
TSI Incorporated, U.S.A.

Kelsall, Julia E.
Johns Hopkins University, U.S.A.

Kleinman, Michael T.
University of California, U.S.A.

Knutsen, Synnove F.
Loma Linda University, U.S.A.

Koenig, Jane Q.
University of Washington, U.S.A.

Lalonde, Francois
Environment Canada, Canada

Langworthy, Lucinda M.
Hunton & Williams, U.S.A.

Lauer, George
ARCO Oil & Gas, U.S.A.

Lee, Jeffrey S.
University of Utah, U.S.A.

Leipold, Wayne H.
Cyprus Miami Mining Corp., U.S.A.

Leonardi, Giovanni S.
Environ. Epidemiology Unit, U.K.

Levy, Drew G.
University of Washington, U.S.A.

Lillquist, Dean
University of Utah, U.S.A.

Linn, William S.
Rancho Los Amigos Med. Ctr., U.S.A.

Lipfert, Frederick
Environmental Consultant, U.S.A.

Lipowicz, Peter J.
Philip Morris, U.S.A.

Lippmann, Morton
NYU Medical Center, U.S.A.

Lunan, Jim
Peabody Holding Company, Inc., U.S.A.

Lund, Loren
Texas Natural Res. Conserv. Comm., U.S.A.

Lundgren, Dale A.
University of Florida, U.S.A.

Lurmann, Fred
Sonoma Technology, Inc., U.S.A.

Lyon, Joseph L.
University of Utah, U.S.A.

Mangelson, Nolan
Brigham Young University, U.S.A.

Mann, Jennifer K.
University of California, U.S.A.

Martin, Thomas E.
ASARCO, Inc., U.S.A.

Mauderly, Joe
Inhalation Tox. Rsch. Inst., U.S.A.

May, Jerry C.
BHP Copper, U.S.A.

McAughey, John
AEA Technology, U.K.

McCleery, Robert E.
University of Utah, U.S.A.

McClellan, Roger O.
CIIT, U.S.A.

McNeill, Dave
Division of Air Quality, Utah, U.S.A.

Menache, Margaret G.
Duke University, U.S.A.

Menotti, David E.
Shaw, Pittman, Potts & Trowbridge, U.S.A.

Meyer, Michael B.
Rupprecht & Patashnick Co., Inc., U.S.A.

Michaels, Robert A.
RAM TRAC Corporation, U.S.A.

Miguel, Ann G.
California Inst. of Tech., U.S.A.

Moolgavkar, Suresh
Fred Hutchinson Cancer Res. Ctr.,U.S.A.

Morrow, Paul E.
University of Rochester, U.S.A.

Noble, Christopher A.
University of California, U.S.A.

O'Keefe, Robert M.
Health Effects Institute, U.S.A.

Obeidi, Fida
Brigham Young University, U.S.A.

Ono, Duane M.
Great Basin Unified Air Pollution
Control District, U.S.A.

Ospital, Jean J.
Southern California Edison, U.S.A.

Ostro, Bart
Calif. Dept. of Health Services, U.S.A.

Packham, Steve
Division of Air Quality, Utah, U.S.A.

Pauluhn, Jurgen
Bayer AG Inst. of Tox., Germany

Paxton, Mary B.
American Petroleum Institute, U.S.A.

Peters, Annette
GSF - Institute fur Epidemiologie, Germany

Peters, John
University of Southern Calif., U.S.A.

Phalen, Robert F.
University of California, U.S.A.

Pichette, Janet
Texas Natural Res. Conser. Comm., U.S.A.

Pinkerton, Kent E.
University of California, U.S.A.

Pope, C. Arden III
Brigham Young University, U.S.A.

Ramsey, Jamie
University of Utah, U.S.A.

Reiss, Rick
Sonoma Technology, Inc., U.S.A.

Ren, Yuan
Brigham Young University, U.S.A.

Rice, James E.
FMC Corp., U.S.A.

Richmond, Harvey M.
EPA, U.S.A.

Rodan, Bruce D.
Karch & Associates, Inc., U.S.A.

Roemer, Willem H.
Dept. of Epid. & Public Health, The Netherlands

Roskelley, Dave
University of Utah, U.S.A.

Ross, Terry G.
Center for Energy & Economic Dev. U.S.A.

Roth, Daniel H.
Roth Associates, Inc., U.S.A.

Salmeen, Irving T.
Ford Motor, Co., U.S.A.

Salonen, Raimo O.
Natl. Public Health Inst., Finland

Samet, James M.
University of North Carolina, U.S.A.

Samet, Jonathan M.
John Hopkins University, U.S.A.

Saperstein, Mark D.
ARCO, U.S.A.

Sarangapani, Ramesh
University of Delaware, U.S.A.

Satin, Kenneth P.
Chevron Corporation, U.S.A.

Scheuch, Gerhard
Inst. for Inhalation Biology, Germany

Schlesinger, Richard
NYU Med. Ctr., U.S.A.

Schum, Michael
University of California, U.S.A.

Schwartz, Joel
Harvard School of Public Health, U.S.A.

Shaw, K.C.
Geneva Steel, U.S.A.

Shea, Quinlan J.
National Mining Association, U.S.A.

Sheppard, Lianne
University of Washington, U.S.A.

Sioutas, Constantinos
Harvard University, U.S.A.

Sisodia, Chatur S.
University of Saskatchewan, Canada

Skapa, Michal
Charles University, Czech Republic

Smith, Kevin R.
Utah State University, U.S.A.

Snipes, Morris B.
Inhalation Toxicology Res. Inst., U.S.A.

Soderholm, Sidney
NIOSH, U.S.A.

Steen, Rodger G.
Air Sciences, Inc., U.S.A.

Steiner, Bruce A.
American Iron & Steel Inst., U.S.A.

Stieb, David M.
Health Canada, Canada

Stöber, Werner
CIIT, U.S.A.

Stuart, Barbara
Washington Dept. of Ecology, U.S.A.

Suh, Helen
Harvard University, U.S.A.

Sullivan, Frank
University of Utah, U.S.A.

Thurston, George
NYU, School of Medicine, U.S.A.

Tillery, Marvin I.
Los Alamos National Laboratory, U.S.A.

Tsai, Shan P.
Shell Oil Company

Turpin, Barbara J.
Rutgers University, U.S.A.

Utell, Mark J.
Univ. of Rochester Medical Ctr., U.S.A.

Valberg, Peter A.
Gradient Corporation, U.S.A.

Valentine, Richard S.
Salt Lake City-County Health Dept., U.S.A.

Van Den Eeden, Stephen K
Kaiser Permanente, U.S.A.

Vardiman, Steven.
Kennecott Utah Copper, U.S.A.

Veranth, John M.
University of Utah, U.S.A.

Vostal, Jaro J.
EHAC, Inc., U.S.A.

Wagner, Gregory
NIOSH/ALOSH, U.S.A.

Wallace, David O.
University of Utah, U.S.A.

Watkins, Ann M.
EPA Acid Rain Div., U.S.A.

Weir, Bruce R.
Systems Applications Intl., U.S.A.

Westerdahl, Dane
California Air Resources Board, U.S.A.

White, Ronald H.
American Lung Association, U.S.A.

White, Russell D.
Chevron, U.S.A.

Wood, Grace
Health Canada, Canada

Wright, Dagan A.
California Public Health Fndn., U.S.A.

Yang, Wei
Washoe County Dist. Health Dept., U.S.A.

Zhang, Junfeng
EMDNJ/Environmental & Occupational
Health Sciences Institute, U.S.A.

Zmirou, Denis
Universite Joseph Fourier, France

Wilson, William
EPA/NCEA, U.S.A.

Woodruff, Tracy
EPA, U.S.A.

Wyzga, Ronald
Electric Power Research Institute, U.S.A.

Zeldin, Melvin D.
South Coast AQMD, U.S.A.

Zhang, Lei
CIIT, U.S.A.

VIII. EVALUATIONS BY PARTICIPANTS

SECOND COLLOQUIUM EVALUATIONS
(Rating 1-5, 5 being best)

	Avg.	SD	N	Comments
Program Quality	4.0	0.7	67	
Program Completeness	4.0	0.7	67	
Discussions	3.6	0.9	67	
Staff	3.6	1.1	64	Colloquium staff were great, hotel staff were so-so
Facility	3.1	1.1	67	
Accommodations	2.7	1.3	63	
Overall	3.9	0.7	65	

Third Colloquium?
Yes = 66; No = 0; Maybe = 2

When?
1.94 years (n=52)

Where?
East Coast = 7; Pk City or other UT = 5; Seattle = 4; N. Carolina = 3; NY or NYU = 3; Calif. = 2; San Antonio = 2; San Francisco = 2; Boston = 2; Las Vegas = 2; Philadelphia = 2; Also, 1 for each of Florida, Tucson, Kansas City, Dallas, Denver, Chicago, Hawaii, Vancouver, Netherlands, Hilton Head Isle.

Note: Several people favored resort-type locations.